THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

NOVEMBER, 1916

ORIGINAL ARTICLES

THE SUSCEPTIBILITY OF MAN TO FOREIGN PROTEINS.[1]

By Warfield T. Longcope, M.D.,
NEW YORK.

(From the Medical Clinic, Presbyterian Hospital, Columbia University, New York.)

Throughout the literature of the last century one may find isolated statements regarding the unexpected effects upon certain individuals of substances now recognized as containing proteins, and perhaps the most significant of these are the observations of Blackley, in 1873, on the effect of grass pollens upon the nasal mucous membrane, conjunctivæ, and the scarified skin of individuals suffering from hay fever. About 1869 and 1870, when transfusions of sheep's blood were much in vogue, it was frequently noted that an urticaria appeared as a late effect of this treatment. It was not, however, until the introduction of diphtheria antitoxin in 1894 that the results of injections of foreign proteins in man received serious study. Lublinski,[2] in the year 1894, described what is now the perfectly familiar picture of serum disease as a sequel to the injection of diphtheria antitoxin, but not until the careful investigations of von Pirquet and Schick,[3] in 1905, was any important light thrown upon the process. They immediately recognized the importance which the so-called antibodies against foreign protein, in this instance horse serum, might have in the production of serum disease,

[1] Lecture delivered before the Harvey Society, New York, February 26, 1916.
[2] Deutsch. med. Wchnschr., 1894, xx, 854.
[3] Die Serumkrankheit, 1905.

and the subsequent observations and experiments by Otto, Rosenau and Anderson, Gay and Southard, Friedemann, Doerr, Friedberger and a host of others[4] have made it quite clear that the introduction of native foreign protein follows essentially the same biological and chemical physical principles in man as in the lower animals.

It is only necessary to point out here that the introduction of the long series of foreign proteins that have been subjected to experiment is followed by the production in the animal body of various antibodies which have the power to unite with the original substance or antigen to produce a new effect. This new effect may be obvious and best studied by mixing antibody and antigen outside the body, as is the case with the hemolysins, the bacterial agglutinins, bacteriolysins, and precipitins; it may be obtained both *in vitro* and *in vivo*, as is the case with antitoxin, or it may be demonstrable almost exclusively in the animal body, as is the case with anaphylaxis.

The bare outlines of the experiments from which our knowledge of anaphylaxis has been derived may be summed up in a statement of the following condition: An animal is injected subcutaneously, intraperitoneally, or intravenously with a small amount of foreign protein, for example horse serum. This produces no visible effect. If, however, after an interval of at least nine to fourteen days, a second injection of the same protein is made the animal becomes ill immediately, presenting characteristic symptoms which differ only slightly for different species; while if the dose of serum is properly gauged and made into the peritoneum or vein the animal dies within five minutes to one hour. This is known as active anaphylaxis. Second, the condition known as passive anaphylaxis, first described by Gay and Southard,[5] Otto[6] and Friedemann,[7] who showed that the blood of an animal sensitized to horse serum confers this specific sensitiveness to a normal guinea-pig. Sensitiveness develops in the normal animal after a period of fifteen to eighteen hours following the inoculation of the serum from the sensitized guinea-pig, and lasts a few days or at most weeks. It is dependent upon the presence in the blood of the actively sensitized animal of antibodies for the specific proteins which are thus transferred passively to the normal guinea-pig. This transfer may take place during pregnancy from mother to offspring. Third, the state termed anti-anaphylaxis by Besredka and Steinhardt,[8] in which

[4] For full bibliography see: Doerr, Wassermann and Kolle, Handb. d. path. Microorg., 1913, ii, 947. Richet, L'Anaphylaxie, 1912. von Pirquet, Arch. Int. Med., f911, vii, 259, 383. Friedemann, Jahresb. u. Immunitätsf., 1910, vi, Abst. i, 31. Besredka, Ibid., 1912, viii, 90. Vaughan, Protein Split Products in Relation to Immunity and Disease, 1913. Rosenau and Anderson, Arch. Int. Med., 1909, ii, 579. Otto, Wassermann and Kolle, Handb. d. path. Microorg., 1908, ii, 255. Auer, Forchheimer's Therapeusis, 1914, v, 39.

[5] Journal of Med. Research, 1907, xi, 143.

[6] München. med. Wchnschr., 1907, liv, 1665.

[7] Ibid., 2414.

[8] Ann. de l'Inst. Pasteur, 1907, xxi, 117, 384.

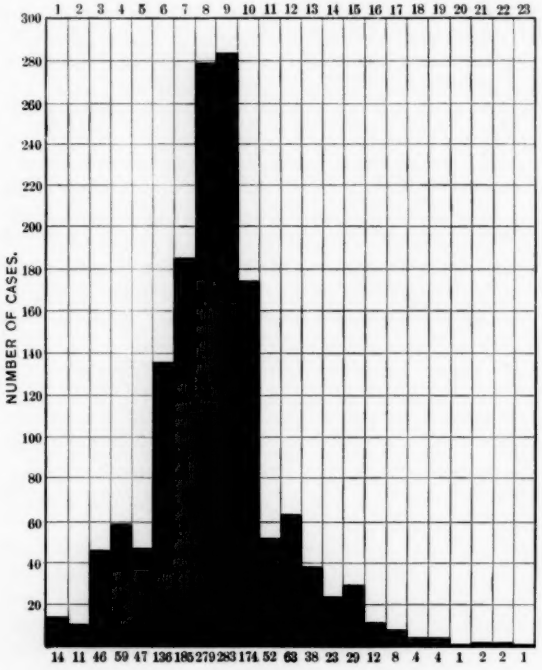
for a short period following the anaphylactic shock the actively sensitized animal becomes insensitive to injections of horse serum. Following this period of anti-anaphylaxis an animal may again become sensitive to the specific protein and remain so for months or years. Finally, it was shown by Rosenau and Anderson[9] that the repeated injection of horse serum at intervals of two or three days produced a refractory condition toward subsequent injections of the specific protein, so that for a long period of time they no longer react to such an injection with anaphylactic symptoms. This refractory state, however, finally gives way to sensitiveness, and eventually the animal is again susceptible. During the refractory state, which has been called one of immunity, antibodies for horse serum may be present in great concentration in the serum, and when injected into normal guinea-pigs will passively sensitize them to the protein.

After this brief statement of the fundamental principles of anaphylaxis it is possible to consider in more detail the process as it develops in man, for the introduction of antitoxic and antibacterial sera has given ample opportunity for an exact analysis of the effect of single and repeated injections of foreign protein. This, as a rule, has been horse serum, though the serum from any foreign species will give the same results. As in an animal, so in man, primary injections of horse serum given by any route produce no immediate symptoms. In the vast majority of instances it remains, as can be shown by the presence of precipitinogen and by anaphylactic methods in the circulation, for long periods of time, and is excreted very slowly, if at all, by the kidneys. For a period of six to ten days following primary injection, known as the incubation period, there is nothing to be observed, but at any moment after the sixth day typical serum sickness may appear. (See Chart.)

The symptoms and signs of this disease are as striking and characteristic as any natural disease process with which we are familiar. Usually a skin eruption with intense itching preceded by glandular enlargement ushers in the attack. The eruption starts, as a rule, at the point of inoculation, but spreads rapidly over the entire body. Urticaria is most common, but there may be a patchy or diffuse erythema, scarlatiniform rashes, or a multiform eruption. Edema of the face and ankles is usual and may affect the entire body. In rare instances it is localized to the pharynx or larynx, and in one instance a transient hemiplegia was supposed to be caused by local edema of the meninges. The temperature is elevated, and there is general malaise and headache with prostration, though rarely nausea or vomiting. Joint pains are very common in severe cases. They are always multiple, and though the pain is exquisite on motion, there is little tenderness and no swelling or reddening.

[9] Bull. 29, Hyg. Lab. U. S. P. H. and M. H. S., 1906; Bull. 36, Hyg. Lab. U. S. P. H. and M. H. S., 1907.

Quite regularly the lymph nodes are enlarged, they are often swollen to the size of walnuts in the region draining the primary injection, and may be excessively tender. The spleen is sometimes enlarged; in 5 to 9 per cent. of the cases there is albuminuria, and, as I shall point out later, there are often disturbances in the functional activity of the kidneys. Examination of the blood, according to von Pirquet, shows a primary polymorphonuclear leukocytosis with subsequent leukopenia and absolute increase in the lymphocytes. The disease



Incubation period in 1493 cases of Serum Disease. Figures at top indicate number of days after injection of serum. Bottom line of figures represents number of cases.

may last for twenty-four hours to twenty days or longer. In the severest cases there are one to four relapses which usually occur after the use of large amounts of serum, and come, according to Axenow,[10] at ten day intervals.

The occurrence, intensity, and duration of the disease depend, upon several factors: First, upon the amount of serum used. The disease is not usual after small doses, but is extremely common

[10] Jahrb. f. Kinderh., 1913, lxxviii, 565.

after large ones. The statistics of Weaver,[11] based on a study of 801 reported cases, show an incidence of 10 per cent. after the injection of 1 to 10 c.c. of serum. Most of the attacks are mild, but the incidence increases in almost direct proportion to the amount of serum used, until, when quantities over 90 c.c. are employed, 75 to 100 per cent. of the patients develop serum disease. Secondly, it seems possible, from the statistics of Bokay[12] and Schulz,[13] that the incidence may depend to some extent upon the source of the serum. Apparently certain horses yield a serum which is much more likely to be attended by serum disease than others. And finally the individual characteristics of the patient play a role, for the same dose of serum from the same source may produce quite different affects in different persons.

A second injection of serum before the tenth day or before the onset of serum disease is not attended by immediate symptoms. It has already been observed that in the case of animals, repeated injections of horse serum at two- to three-day intervals produce a condition which makes them refractory to subsequent injections, which state may last many weeks. By the same method in human beings the incubation period for serum sickness may be prolonged for weeks, but its final appearance cannot always be prevented, and after these multiple doses at short intervals the attack, when it appears, is, according to Goodall,[14] especially severe. If, however, a second injection is made after the tenth day, von Pirquet and Schick have shown that the following reactions may occur: (1) The local immediate reaction. Within fifteen minutes to an hour after subcutaneous injection of serum, edema, erythema, or urticaria appears at the site of inoculation. (2) The general immediate reaction which is characterized by a more or less severe general reaction coming on within twelve to twenty-four hours after the inoculation and having the characteristics of a fulminant case of serum sickness. The most violent and general immediate reactions are accompanied by such symptoms as dyspnea of asthmatic type, cyanosis, collapse, nausea and vomiting, and suppression of urine, symptoms which are not regularly seen in the ordinary form of the disease. (3) The accelerated reaction or form in which the incubation of the serum sickness falls between the immediate reaction and the ordinary reaction and comes on within a period of three to five days after inoculation, and finally the second injection may be followed simply by the normal form of serum sickness. Any of these reactions may occur separately or may be combined in one and the same patient.

The actual occurrence of the immediate general reaction following

[11] Arch. Int. Med., 1909, iii, 485.
[12] Deutsch. med. Wchnschr., 1911, xxxvii, 9.
[13] Berl. klin. Wchnschr., 1914, li, 349, 401.
[14] Jour. Hyg., 1907, vii, 607; British Med. Jour., 1913, ii, 1359.

a second injection varies according to different observers. It is noted most often, according to von Pirquet and Goodall, between the thirty-fifth and eightieth day after the primary inoculation of serum, and occurs when serum is injected in large quantities at this period in about 60 per cent. of the cases. An injection made after three months is usually followed by an accelerated reaction, and when years have elapsed the general reaction may be of the ordinary type. The immediate reaction, though it may be severe, has, as far as I know and as the statistics of Park[15] and Nemmser[16] and Cuno[17] show, never caused death when the inoculation is made subcutaneously. Following a second intravenous injection, however, Koch[18] has reported one death. After the second injection of serum made in the spinal canal, coma, convulsions, and death have been reported by Hutinel,[19] Grysez and Dupuich,[20] and Archard and Flandin.[21] Auer[22] has recently analyzed all these cases and considers that death is not due to true anaphylactic shock. The symptoms are certainly not those of a general immediate reaction, but it seems possible that a local immediate reaction may occur, similar to that in the skin which might produce extensive edema of the meninges, and in this way account for the symptoms as they are described.

The local immediate reaction upon second injection is specific, as was shown by von Pirquet, and is analogous to the Arthus phenomenon in the rabbit. Lucas and Gay[23] describe it as a very frequent occurrence in children receiving prophylactic doses of diphtheria antitoxin at three weeks' intervals. Moss,[24] in 1910, drew attention to the value of this immediate cutaneous reaction in determining the presence of sensitiveness to horse serum in persons who had previously been injected and found that five of twenty-one such patients reacted positively to an intracutaneous injection of horse serum two to three years after the primary injection. The exact time of appearance of this immediate reaction for skin sensitiveness has been studied by Hamburger and Pollok,[25] Michaels,[26] and Cowie.[27] By making intradermic injections of 0.1 to 0.5 c.c. of serum at short intervals these observers have noted its appearance on the fifth day after the injection of serum and its persistence for years after. Michaels makes the important observation that the

[15] Tr. Assn. Amer. Phys., 1913, xxviii, 95.
[16] Deutsch. med. Wchnschr., 1913, xxxix, 740.
[17] Ibid., 1914, xl, 1017.
[18] Berl. klin. Wchnschr., 1915, lii, 685.
[19] Presse méd., 1910, xviii, 497.
[20] Bull. et mém. Soc. méd. d. hôp. de Paris, 1912, xxxiii, 371.
[21] Compt. rend. Soc. biol., 1912, lxxiii, 419.
[22] Forchheimmer's Therapeusis, 1914, v, 39.
[23] Jour. Med. Research, 1909, xx, 251.
[24] Jour. Am. Med. Assn., 1910, lv, 776.
[25] Wien. klin. Wchnschr., 1910, xxiii, 1161.
[26] Arch. Mal. d. Enfants, 1913, xvi, 835.
[27] Am. Jour. Dis. Child., 1914, vii, 253.

reaction cannot be obtained during serum sickness, and in two instances when it was possible to obtain a positive skin reaction before the onset of the disease it disappeared during the course of the serum sickness. Immediately after the serum sickness all observers agree that the skin reaction rapidly increases in intensity, and when the test is properly performed it is obtained in 80 to 90 per cent. of the cases even for years after.

Dr. Rackamann and I have employed this method to determine the development of skin sensitization in serum disease. The test dose has been very small and injected intradermally, 0.02 c.c. of pure serum and of serum in $\frac{1}{10}$ and $\frac{1}{100}$ dilutions has been employed. After these minute doses skin sensitiveness does not appear until serum disease has set in, but once having made its appearance the reaction increases in intensity and has been present by the fifteenth to twentieth day in most instances. A reaction of equal intensity has been obtained in several adults two or three years after an injection of antitoxin. The intradermal method is much the most sensitive of any of the cutaneous tests, and may be strikingly positive with serum in $\frac{1}{100}$ or $\frac{1}{500}$ dilution, although the scarification method such as used for tuberculin by von Pirquet gives a negative response with undiluted serum. It is, as far as we have observed, specific and cannot be brought about in these cases by the use of various other animal sera, egg-white, casein, or vegetable proteins. It consists in the appearance after a period of ten to fifteen minutes of an elevated, yellowish, firm wheal, surrounded by a bright red erythematous areola. This increases rapidly in size until the wheal reaches at the end of thirty to forty-five minutes 1 to 2 cm. in diameter, and the erythematous zone 3 to 6 cm. in diameter. During this period the patient often complains of itching at the site of inoculation. At the end of an hour the reaction fades and in twelve hours nothing is to be seen. Salt solution, human sera, and various other animal sera result in the formation of a minute white papule 5 to 6 mm. in diameter, about which there may appear a narrow red zone. This traumatic reaction fades in five to fifteen minutes, and is almost invisible at the end of half an hour when the true reaction is at its height. Knox, Moss, and Brown[28] have found that under similar conditions a skin reaction is obtained in the rabbit. It makes its appearance first on the eleventh day after primary inoculation of serum, and is present in most cases by the sixteenth to twenty-second day. It differs from the reaction in the human being in that the development is much slower, attaining its height only after twelve to twenty-four hours, while it persists much longer, lasting two or three days. The skin reaction must be considered as a delicate and probably specific reaction of an individual artificially sensitized to a foreign protein, and makes its appearance from five to fifteen days after the primary injection.

[28] Jour. Exp. Med., 1910, xii, 562.

At about the time that this sensitiveness appears, and sometimes immediately before the onset of the serum disease, other reactions occur which are considered evidence of the formation of antibodies to the foreign protein. These are represented by the appearance in the blood serum of precipitins for the foreign protein and the substance which is capable of transmitting the sensitive state passively from one animal to the other. Hamburger and Moro,[29] who first demonstrated precipitins for horse serum in the blood of cases of serum disease, and Doerr and Russ,[30] as well as Weil,[31] experimenting later in animals, have attached much importance to the precipitins as a part of the anaphylactic reaction, though von Pirquet was inclined to regard the production of precipitins as an accompanying phenomenon rather than as one upon which anaphylaxis is dependent. C. Wells,[32] has followed the curve of production of these antibodies during serum sickness in children receiving diphtheria antitoxin. In some cases precipitins are demonstrable about the sixth day after injection of serum and before the sickness starts, but with the onset of serum sickness the precipitins diminish or disappear to increase rapidly after the disease to a high degree of concentration. A diminution again takes place sixteen days later, and finally the precipitins can no longer be demonstrated.

More closely related to the anaphylactic state than the precipitin is the presence of the substance which is capable of causing passive sensitization, variously designated immune substance, anaphylactic antibody, anaphylactin, or allergin. Though Doerr and Russ[33] have undertaken to measure quantitatively the amount of this antibody in a given specimen of serum, there are certain factors, as has recently been shown by Lewis,[34] which complicate such a quantitative analysis of the anaphylactic antibody, and consequently the result obtained from passive transfer can only roughly measure the actual amount of this substance in the actively sensitized animals. That there is some parallelism between the amount of precipitin and quantity of anaphylactin has been shown by Burkhardt,[35] but when several injections of serum are given to sensitize actively the two reactions do not run parallel. Weill, Hallé, and Lémaire[36] found that the blood of rabbits receiving a single injection of horse serum showed the power to transmit the anaphylactic antibodies to guinea-pigs after the lapse of ten days. This increased in intensity up to the twenty-fifth day, and gradually disappeared after the sixtieth day. When, however, repeated injections of horse serum were employed

[29] Wien. klin. Wchnschr., 1903, xvi, 445.
[30] Ztschr. f. Immunitätsf., orig., 1909, iii, 181. Doerr, Wassermann and Kolle, Handb. d. path. Microörg., 1913, ii, 947.
[31] Jour. Immunol., 1916, i, 1, 19, 35, 47.
[32] Jour. Inf. Dis., 1915, xvi, 63.
[33] Loc. cit.
[34] Jour. Inf. Dis., 1915, xvii, 241.
[35] Ztschr. f. Immunitätsf., orig., 1910, viii, 87.
[36] Compt. rend. Soc. de biol., 1908, lxv, 141.

at two months' intervals the ability of the rabbits' serum to sensitize guinea-pigs appears immediately after the last injection, but does not persist as long. Anderson and Frost[37] found that the blood of guinea-pigs contained "anaphylactin" for as many as four hundred and fifty days after sensitization, and as Rosenau and Anderson originally noted, guinea-pigs made refractory to anaphylactic shock by repeated injections of horse serum, still carry in their serum anaphylactic antibodies in large amounts. Attempts to demonstrate this phenomenon in man have met often with indifferent success. Anderson and Frost,[38] as well as Archard, Flandin,[39] Weil,[40] and Yamanouche[41] report isolated successful results, but Novotny and Schick[42] obtained positive results in only 2 out of 12 cases. Gryez and Bernhard,[43] however, were more successful, and with the blood drawn from eleven children five to two hundred and thirty-four days after injection of diphtheria antitoxin were able to sensitize guinea-pigs passively to horse serum. Dr. Rackamann and I have made some observations upon the appearance of this anaphylactic antibody in ten individuals receiving horse serum. We have found that the anaphylactin was present in one or two instances before the appearance of serum disease, but in the vast majority of cases it is only demonstrable at the subsidence of the symptoms. Once having appeared at this time, however, it may persist for many days and be present in such concentration that one can readily transfer the sensitiveness from man to a guinea-pig.

It will thus be seen that toward the end of the incubation period of serum disease, certain antibodies and immune reactions, namely, the skin reaction, the precipitin reaction and anaphylactin, can occasionally be demonstrated in the blood serum. With the appearance of the symptoms they diminish or disappear to reappear with great intensity at the subsidence of the attack. Since the serum or antigen during this entire period may still be demonstrated in the circulation, it is highly probable, as was proposed by von Pirquet, that serum disease is brought about by a union of the rapidly forming antibodies and the circulating antigen. The theoretical explanation as to the place and cause of this union has been the subject of much discussion. The union, of course, may take place in the circulating blood, thus liberating toxic substances that produce the symptoms of serum disease or anaphylaxis; second, the union may occur in the tissues and cells of the body; or, third, it may proceed in both situations. Friedberger, who has experimented extensively along this line, has advanced first one and then the other view, and in the human being the appearance of precipitins and the anaphylactic

[37] Bull. 64, Hyg. Lab. U. S. P. H. and M. H. S., 1910.
[38] Loc. cit.
[39] Loc. cit.
[40] Proc. Soc. Exp. Biol. and Med., 1914, xii, 37.
[41] Compt. rend. Soc. de biol., 1910, lxviii, 1000.
[42] Ztschr. f. Immunitätsf., orig., 1909, iii, 671.
[43] Comp. rend. Soc. de biol., 1912, lxxiii, 387.

antibodies in the blood stream before the onset of serum disease, might lead one at first to suppose that the reaction was principally in the circulating blood, as was the original idea of von Pirquet. The observations of Pearce and Eisenbrey,[44] of Schulz[45] and those of Dale,[46] which have been extensively amplified and confirmed by Weil,[47] show definitely that the cells of sensitized animals, and certainly the smooth muscle of the uterus, freed from all traces of the body fluids, are capable of reacting violently when brought in contact with the specific antigen toward which the animal is sensitive. The original observation of Rosenau and Anderson repeatedly confirmed that the blood serum of an animal made highly refractory by repeated injections of horse serum may still contain large amounts of anaphylactic antibody, is in support of the idea at present quite widely accepted that the presence of these antibodies in the serum is a source of protection rather than harm. Circulating in the blood in large quantities they unite slowly with the reinjected antigen or at least "fix" it so that the antigen as such is prevented from coming in contact with the cells of the body. The facts which have been brought out in the study of serum disease in man might be interpreted in the light of either theory.

The onset of serum disease is probably, therefore, a visible evidence of the development of general sensitiveness and represents a more or less violent reaction between the circulating antigen and antibody which is in process of development, certainly in the cells, but possibly too in the circulating blood. It is followed by a rapid expulsion of antibodies into the circulation, and shortly afterward by a period of hypersensitiveness, at which time the reinjection of serum may call forth a violent general reaction. Subsequently this period of hypersensitiveness diminishes and antibodies may disappear from the circulation. The injection of serum at this time, owing to the slight concentration of antibodies, does not produce an immediate general effect, but excessive antibody formation under these circumstances, as von Pirquet and von Dungern have shown in the case of precipitins, is much more rapid than in the normal individual and the general reaction, or accelerated serum sickness, appears. Finally, with a complete loss of sensitiveness, the individual returns to the normal state and the reaction is of the normal type.

There is not time to discuss the question as to whether the union of antibody and antigen is of chemical nature, whether it depends upon fermentation, or whether, as is the view that Zinsser[48] has brought forward, some change in the physical properties of the serum determines the union of these two substances. To elucidate the

[44] Tr. Cong. Am. Phys. and Surg., 1910, viii, 402.
[45] Jour. Pharmacol. and Exp. Therap., 1910, i, 549. Bull. 80, Hyg. Lab. U. S. P. H. and M. H. S., 1912.
[46] Jour. Pharmacol. and Exp. Therap., 1913, iv, 167.
[47] Jour. Med. Research, 1914, xxx, 87, 299.
[48] Arch. Int. Med., 1915, xvi, 223.

actual nature of the toxic substance that is formed by this union, much thought and experimentation have been expended. It is only a step from the early observations of Pfeiffer,[49] and Wolff-Eisner[50] upon the poisonous products of bacterial disintegration to the work of de Waele,[51] Biedl and Kraus,[52] Vaughan,[53] Friedberger,[54] Weichardt and Schittenhelm,[55] and many others who have shown that the products and by-products of protein digestion when injected into various animals may cause symptoms almost identical with true anaphylactic shock. These observations soon suggested that with the union of antibody and antigen the antigen or foreign protein is digested to form poisonous split products. To confirm this idea evidence has been brought forward by Abderhalden,[56] Cammerer and Pincussohn,[57] by Pfeiffer and Jarish,[58] G. Zung and György[59] and by Jobling and Petersen,[60] to show that during anaphylactic shock in dogs products of protein digestion appear and that the non-protein nitrogen, together with the proteose of the serum, are distinctly increased.

So far we have discussed only artificial sensitization in man, but it is now necessary to direct attention to a state in which sensitiveness to foreign proteins exists without the known introduction of these proteins. It has been repeatedly observed that the first injection of any foreign serum may be attended in man by a violent immediate reaction. One of the earliest instances to come into prominent notice was the immediate death of Prof. Langerhans's young son after receiving for the first time an injection of diphtheria antitoxin. Gottstein[61] reported a few such cases in 1896, and in 1909 Gillette[62] collected from the literature 30 in which sudden collapse or death followed immediately upon the first injection of antitoxin. It is important to note that 22 of these cases gave a history of asthma or of some respiratory disease. The patient immediately after the injection shows great uneasiness; perhaps complains of constriction in the chest; has violent dyspnea; the face swells and becomes purple; he falls in collapse and may be dead in five to ten minutes. In attacks which are somewhat less fulminant there is violent asthma, cyanosis, collapse, and a giant urticarial eruption. These perhaps are the most striking and certainly terrific demonstrations of spontaneous sensitiveness to foreign protein, but they only repre-

[49] Ztschr. f. Hyg. u. Infektionkrankh., 1892, xi, 293.
[50] Centralbl. f. Bakt., 1904, xxxvii, 390, 566, 684.
[51] Bull. Acad. Roy. de Méd. de Belgioue, Brux., 1909.
[52] Wien. klin. Wchnschr., 1909, xxii, 363.
[53] Loc. cit.
[54] Ztschr. f. Immunitätsf., orig., 1911, ix, 369.
[55] Ztschr. f. exp. Path. u. Therap., 1912, x, 412, 448; xi, 69.
[56] Ztschr. f. physiol. Chem., 1912, lxxxii, 109.
[57] Ibid., 1909, lix, 293.
[58] Ztschr. f. Immunitätsf., orig., 1912–13, xvi, 38.
[59] Ibid., 1915, xxiii, 402.
[60] Jour. Exp. Med., 1915, xxii, 401.
[61] Therap. Monatsh., 1896, x, 269.
[62] New York State Med. Jour., 1909, ix, 373.

sent one of the many such sensitizations which have been long recognized as idiosyncrasies. The early work in 1873 of Blackley[63] upon hay fever I have already mentioned. It is of considerable historical interest to note that he associated this condition as early as 1853 with the inhalation of pollen grains, and showed definitely that the instillation of certain pollens in the nose and eye produced in hay fever patients edema and congestion of the mucous membrane with lacrimation. He also made the important observation that pollen grains rubbed into a scarification of the skin called forth an intense itching and local edema. The work of Dunbar,[64] in 1903 and 1904, showed that this was a specific reaction, and later Weichardt[65] brought out the fact that it was due to the protein of the pollen. From this it was only a step for Wolff-Eisner,[66] in 1906, to suggest that hay fever had its origin in sensitization to proteins of various pollens, and later to apply this principle to the explanation of the origin of the urticarias succeeding the ingestion of certain foods.[67]

So common, indeed, is this conception of protein sensitization that attempts have been made to explain thereby all physiological and pathological processes from childbirth to epilepsy. But in spite of these unwarrantable views it is certainly an important factor in some pathological processes, and for this reason it is highly essential that we should understand accurately what true protein sensitization means and analyze the hypotheses that may be evolved from this fascinating but very obscure subject.

A survey of the literature brings forth many interesting examples of what seem to be true spontaneous susceptibility to various foreign proteins. The symptoms produced from contact with these proteins are usually referred to the respiratory tract, the gastro-intestinal tract, and the skin. Hay fever is the example of protein sensitization most thoroughly studied in which the symptoms brought on by contact with foreign proteins are usually confined to the respiratory tract and the conjunctivæ. In a certain proportion of cases of asthma the attack simulates, as the fundamental experiments of Auer and Lewis[68] suggested to Meltzer,[69] mild anaphylactic shock in the guinea-pig, and as has been demonstrated since, it may be precipitated by inhalation, subcutaneous injection, or ingestion of foreign proteins to which the individual is sensitized. The most striking examples are to be found in the patients whose attacks invariably occur when they come in close contact or even in the near vicinity of such animals as horses, dogs, cats, rabbits, or mice; or

[63] Experimental Researches on the Cause and Nature of Hay Fever, London, 1873.
[64] Deutsch. med. Wchnschr., 1903, xxix, 149.
[65] Centralbl. f. Bakt., 1906, xxxviii, 493.
[66] Dermat. Centralbl., 1907, x, 164.
[67] Wolff-Eisner, Das Heufieber. München, 1906.
[68] Jour. Exp. Med., 1910, xii, 15.
[69] Tr. Assn. Am. Phys., 1910, xxv, 66.

in patients who develop from their hay fever true paroxysms of asthma. The subcutaneous injection of even the minutest quantities of solutions of these proteins will precipitate violent paroxysms of asthma, and it is in such spontaneously sensitized individuals that the first injection of diphtheria antitoxin has produced violent symptoms or death.

The gastro-intestinal disturbances dependent upon sensitization to eggs, which is not uncommon in children, and may occur in adults, has been studied, especially by Schloss,[70] Lesné and Richet fils[71] and Talbot.[72] Sensitization to cow's milk, as recently pointed out by Kleinschmidt[73] is another cause of gastro-intestinal disturbances in children. H. L. Smith[74] first drew attention to the importance of sensitization in a case of buckwheat poisoning and similar symptoms after eating such foods as strawberries, melons, or other fruits or vegetables, certain form of meats and shellfish, are widely recognized and are familiar as idiosyncrasies.

Various skin eruptions are associated with direct or indirect contact with foreign protein. In some instances an urticarial eruption always follows contact with the fur of one or another animal or the juice of plants. Wechselmann[75] has described a form of dermatitis which comes on in satinwood workers ten to fourteen days after they start their work. Talbot and Lesne and Richet have especially called attention to eczema which so frequently is seen in children sensitive to egg-white and milk. An increased susceptibility which Goldschmidt[76] has described, to the irritating odor and juices coming from the living ascaris, is probably to be classed with these cases.

A few instances of hypersensitiveness to the sting of insects are described. I know of one individual in whom the sting of the mosquito produces enormous areas of edema similar to the so-called angioneurotic form, and in another case a sting of a wasp was followed by symptoms exactly like the immediate reaction in serum disease. Great local swelling with erythema and edema, collapse, general urticaria; joint pains appeared immediately on two occasions after this individual was stung. Finally, there is a very definite group of cases, of which I have seen several, in whom suddenly, without assignable cause, the patient is stricken with an illness which is precisely like serum disease, and which may recur at the end of several months. At the onset there may or may not be nausea and vomiting, but always there is a general urticaria associated with slight fever, swollen tender lymph nodes, arthralgia, and usually a mild albuminuria. Indeed, some of the attacks of Hen-

[70] Am. Jour. Dis. Child., 1912, iii, 341.
[71] Arch. d. mal. d. infants, 1913, xvi, 81.
[72] Boston Med. and Surg. Jour., 1914, clxxi, 708.
[73] Monatsh. f. Kinderh., 1913, xi, 644, orig.
[74] Arch. Int. Med., 1909, iii, 350.
[75] Deutsch. med. Wchnschr., 1909, xxxv, 1389.
[76] München. med. Wchnschr., 1910, lvii, 1991.

nock's purpura are not unlike serum disease, and we have found at least one case sensitive to several foreign proteins. Even more obscure pathological processes, such as eclampsia, have been explained upon the basis of protein sensitization, in this instance, to the chorion or fetal tissues; but the evidence for such assumptions at the present time does not admit of further discussion of these very obscure conditions.

Reference must be made here to the interesting drug susceptibilities which apparently may be spontaneous or acquired after the repeated subcutaneous or intravenous use of certain chemicals. In this connection reactions to the iodin and arsenic compounds have been most carefully studied. Stäubli[77] and Kaufman[78] have called attention to the increasing local inflammation which patients are likely to experience after repeated injection of cacodylate salts. With the introduction of salvarsan many observers have noticed anaphylactic-like symptoms during the intravenous administration of this drug. Iwaschenzoff[79] has reported many such instances, and Draper,[80] who has observed it in about 55 per cent. of all treated cases, states that it is never noted at the first injection, rarely at the second, and that if it occurs at all it usually does so at or after the fourth. The patient complains of oppression in the chest, is restless, has dyspnea, shows suffused face and conjunctivæ, and cyanosis. Afterward there may be vomiting and occasionally a blotchy urticaria appears.

Up to the present time it is not known that antibodies are produced by any substances other than those which contain a high protein molecule, and at first the explanation of these reactions was difficult. Friedberger and Ito[81] have called attention to the fact, however, that the serum of a guinea-pig may be so altered by treatment with the tincture of iodin that a mixture of the two will sensitize the guinea-pig to subsequent injections of the same mixture of its own serum and iodin or sodium iodin or to Logul's solution. A first injection of Lugol's solution sensitizes to this mixture of serum and iodin but not to potassium iodin or to Lugol's solution alone. Swift[82] has been able to obtain essentially the same results with salvarsan, and the explanation given by these observers for the iodiosyncrasies to iodides and the anaphylactic-like symptoms after the intravenous injection of salvarsan is that the combination of the drug with the patient's serum forms a new protein compound to which he may be actively sensitive. The reports by Bruck[83] and Klaussner[84] of passive sensitization with the serum of patients

[77] Deutsch. med. Wchnschr., 1912, xxxviii, 2452. [78] Ibid., 1913, xxxix, 272.
[79] München. med. Wchnschr., 1912, lix, 806.
[80] Jour. Am. Med. Assn., 1916, lxvi, 400.
[81] Ztschr. f. Immunitätsf., orig., 1912, xii, 241.
[82] Jour. Am. Med. Assn., 1912, lix, 1236.
[83] Berl. klin. Wchnschr., 1910, xlvii, 517, 1928.
[84] München. med. Wchnschr., 1910, lvii, 1451; 1983. 1911, lviii, 138.

showing drug idiosyncrasies have been disproved by Zieler[85] and Pöhlmann.[86]

These examples, and they might be multiplied many times, represent a group of morbid conditions which have received most study up to the present time. A careful comparison of the symptoms following an injection of foreign protein in the sensitized man with those seen in various animals during anaphylactic shock shows a close similarity. The multiplicity of symptoms is greater in man than in any other one animal. But even typical serum disease has been observed in calves by Beclere, Chambon, and Menard,[87] and in rabbits we have noticed enlargement of the lymph nodes with subcutaneous edema from the sixth to the tenth day after intravenous injection of large quantities of horse serum.

Besides this similarity between the symptoms in man and animals there is a close analogy between the development of specific immune bodies in the two species. This was especially emphasized in considering serum disease, and the same type of immune bodies has been shown to exist in the spontaneously sensitized individual.

Precipitins to cow's milk have been found in the serum of nurslings by Kleinschmidt, and Clowes[88] and Koessler[89] have noted precipitins for pollen in the serum of hay fever patients. Bruck[90] was able to sensitize guinea-pigs passively to pig serum with the blood of a patient who developed violent gastro-intestinal spasm and urticaria after eating pork. Similar results were obtained by Schloss[91] with the serum of his patient, who was sensitive to egg-white, and by Koessler with the serum from cases of hay fever.

The specific skin sensitiveness which is obtained in immune rabbits and guinea-pigs, and which is a characteristic of the artificial sensitization by antitoxic sera in the human being, is an especially prominent feature of the spontaneously sensitized.

The application of minute quantities of specific protein to the skin of such a patient causes a severe local urticaria and erythema, and just as the skin reaction has been employed to estimate the degree and persistence of sensitization in people subjected to one or two injections of antitoxic sera, so it has been used now quite extensively by Schloss, Talbot, Koessler, Cooke,[92] Goodale[93] and others to determine the protein to which these people may be sensitive. There can be no doubt that the skin sensitiveness is solely dependent upon the introduction of protein, for Schloss obtained cutaneous reactions in his case of egg idiosyncrasy with pure ovamucin, ovoglobulin, ovoalbumin, and ovomucoid. We, too, have obtained striking skin

[85] München. med. Wchnschr., 1912, lix, 401; 1641.
[86] Ibid., 1914, lxi, 543.
[87] Ann. d. l'Inst. Pasteur: 1896, x, 567.
[88] Proc. Soc. Exp. Biol. and Med., 1913, x, 69.
[89] Forchheimer's Therapeutsis, 1914, v, 671.
[90] Arch. f. Dermat., 1909, xcvi, 241.
[91] Loc cit.
[92] Laryngoscope, February, 1915.
[93] Boston Med. and Surg. Jour., 1914, clxx, 837.

reactions with chemically pure phaseolin, prepared from beans and kindly sent us by Profs. Mendel and Osborne, of Yale.

An analysis of the conditions of sensitiveness in these patients, however, shows that they differ in some respects from the artificially sensitized. In the first place the degree of hypersusceptibility is generally much greater than is ever reported in the artificially sensitized. In the second place the sensitization is usually multiple, and in the third place the method of sensitization is problematical.

Not only is the increased susceptibility seen in the general violent reactions following subcutaneous and intravenous injections of the specific proteins which may be so great that a subcutaneous injection of 1 c.c. of 1 to 1000 dilution of serum, or as stated by Koessler, 1 c.c. of a 1 to 50,000,000 dilution of pollen extract will bring about general urticaria and asthma, but it is also noticeable in the response of the skin and mucous surfaces. Patients artificially sensitized with horse serum rarely develop horse asthma, though such a thing is possible, for Sewall[94] reports an attack of rabbit asthma in a man who has been injected with rabbit serum. Mere contact with horses will not produce anaphylactic symptoms in guinea-pigs sensitized to horse serum, though instillation of serum into the nose or trachea will do so. Even rarer are gastro-intestinal symptoms following ingestion of proteins to which either man or animal has been actively and artificially sensitized. In the sensitized guinea-pig numerous observers have attempted to produce shock by way of the gastro-intestinal tract, but all have met with complete failures. We have seen, on the other hand, that gastro-intestinal symptoms are common in the individual with spontaneous sensitization. The relative susceptibility of the skin and mucous membranes in these individuals may, however, vary greatly, and though the inhalation or intradermic injection of foreign protein may bring about general urticaria and asthma, ingestion of the same protein may be absolutely harmless and without the slightest effect upon the gastro-intestinal mucosa. Thus one of our asthmatics whose skin was highly sensitive to sheep serum and who on several occasions developed urticaria and asthma after a minute subcutaneous injection, could take by mouth large quantities of sheep serum without the slightest gastro-intestinal symptoms.

The second point of difference, namely, the multiple sensitiveness, is very difficult to interpret. Whereas the artificial sensitization of both man and animals is within limits specific, these patients frequently give a history not only of idiosyncrasies to more than one substance, but as most observers who have studied their skin reactions have noted, give positive skin tests to several different proteins. In the patients whom Dr. Rackamann and I have investigated, this has been quite regularly noted. We have found, however,

[94] Arch. Int. Med., 1914, viii, 856.

that the skin reaction and occasionally the general reaction is limited to certain groups of proteins. Patients can thus be roughly classified as those who react to the sera of animals, those who react to eggs or the sera of fowls, those who react to the extract of shellfish, and those that react to the protein of plants. Occasionally the same individual may show sensitization to two or three groups, but, as a rule, it is confined to one. These reactions, too, we have found are not limited solely to abnormal patients, since in a long series of apparently healthy individuals we have found two or three who show skin sensitiveness to two or more foreign proteins.

It is, of course, possible, as was shown early by Rosenau and Anderson, to sensitize the guinea-pig to at least three different proteins, to each one of which the animal will react specifically, and one might suppose the same could easily happen to human beings once the path to sensitization was open. Besides this it is known, that only within certain limits is the anaphylactic reaction specific inasmuch as guinea-pigs highly immune to the serum of one animal will show mild anaphylactic symptoms when injected with the serum of a closely allied species. This is especially true for man and ape, horse and ass, while Wells and Osborne[95] have shown that the same is true of plant proteins, for an interanaphylactic reaction takes place between chemically pure gliadin from wheat and hordein from barley.

The wide range of sensitiveness, however, and the great unlikelihood that the person might come in contact with many of these proteins, makes it very doubtful whether this, which is accepted by some as an explanation, is correct.

A second possibility, namely, that the sensitization is nonspecific, must be considered. It is known that when native proteins are heated or brought into contact with alkalies or other chemical agents their physical properties are injured and they no longer give specific biological reactions. References has already been made to the effect that iodin and salvarsan may have. The protein under these circumstances is said to be denatured. By this process of denaturizing, Landsteiner and Prasek[96] were able to destroy partially the specific precipitin reaction to horse serum. It is possible to conceive, therefore, that during a natural process of sensitization, through whatever route, the native protein is denatured, and when it comes in contact with the cells and tissue juices, produces a nonspecific sensitization. This might be especially true if the protein enters the body by way of the gastro-intestinal tract, and is accepted as the explanation by Otto and Hoefer.[97]

Although the mode of sensitization might seem at first glance easy to explain, there are certain factors involved that really make its

[95] Jour. Inf. Dis., 1913, xii, 341.
[96] Ztschr. f. Immunitätsf., orig., 1914, xx, 211.
[97] Ztschr. f. Hyg. u. Infektionskrankh., 1915, lxxx, 1.

interpretation very difficult. The paths open for such a sensitization are, of course, numerous. Wounds of the skin and mucous membranes might readily be held responsible, and even through the unbroken mucous membrane sensitization may be accomplished in animals. The history of many of these cases of spontaneous sensitization suggests that the process has taken place by one of these routes. But such an explanation is not applicable to all cases, and cannot account for the fact that an infant shows violent symptoms the first time it is fed an egg.

The history of idiosyncrasies in certain families, such as the tendency to asthma or hay fever, or the susceptibility to certain foods, has long been recognized as very common. Cooke obtained a history of some idiosyncrasies in the immediate families of 129, or 63.8 per cent., of 205 cases of hay fever, and everyone who has written on the subject of asthma draws attention to the familial tendency, Lesné and Richet report the occurrence of egg sensitiveness through three generations. Inheritance must, therefore, be considered as a possibility. Immunity to certain poisons may be transmitted from mother to offspring, and it has been definitely shown by Rosenau and Anderson,[98] Gay and Southard,[99] and by Lewis[100] that the same is true of hypersensitiveness to horse serum in guinea-pigs. Hypothetically this may take place in one of three different ways: as true inheritance through the germ plasm of the cells, either of the father or mother; second, by direct influence of the immunizing agent that affects the mother, upon the cells of the fetus, which would produce active immunity in the child. Third, by passive transference of the immune bodies from mother to fetus by way of the blood or milk.

It was shown by Ehrlich[101] in studying the transmission of abrin and ricin immunity in mice that this is conferred only by the mother, and that even when the mother is immunized during pregnancy the immunity in the offspring lasts but a few weeks. He concluded that this was, therefore, in no sense of the word a true inheritance, but the passive transference to the fetus or child of immunity through the blood or milk of the mother. The immunity is not transmitted to the second generation. The same principle has been established in the transference of other forms of immunity and in experimental anaphylaxis. Groer and Kassovitz[102] have concluded from a recent study that the antitoxin for diphtheria, which Schick showed was present in the blood and tissues of many human beings was transmitted passively from mother to infant through the placenta. The facts so far collected regarding the familial tendency of idiosyncrasy to foreign protein

[98] Loc. cit.
[99] Loc. cit.
[100] Jour. Exp. Med., 1908, x, 1; 608.
[101] Ztschr. f. Hyg. u. Infectionskrankh., 1892, xii, 183.
[102] Ztschr. f. Immunitätsf., orig., 1914, xxiii, 108.

do not accord absolutely with those observed in experimental transference of immunity and anaphylaxis from mother to offspring. In the first place, sensitization in man is not transient but often of years' duration. In the second place it may occur through four generations, and in the third place it is often noticeable principally or solely, as occurred in the extraordinary family described by Laroche, Richet and St. Girons,[103] in the male members. And finally, the sensitization may not always be to the same protein. In at least one family which we studied the father was sensitive to horse serum and the son to egg-white. If inheritance is a factor, therefore, it cannot be by means of passive transfer from mother to infant, but in some instances, at least, may be a true inheritance of cell characteristics derived either from the father or mother. The whole problem, since it is one of greatest importance, needs careful study, but one is almost inclined to suggest that occasionally sensitization toward foreign protein may be an inherited characteristic of the cell plasm and often not highly specific in character. Whether this is dependent upon the presence of true antibodies to the foreign protein or ferments, as Abderhalden and others have suggested, it is impossible to say. That receptors in the sense of Ehrlich for sheep cells may reside in the organs of such species as lobsters, crabs, chickens, and dogs, has been shown by Amako,[104] and more important still is the demonstration of von Dungern and Hirschfeld[105] that the isoagglutinins are inherited and transmitted strictly according to Mendelian law.[106]

The high degree of susceptibility in some people with spontaneous sensitiveness, the multiplicity or lack of specificity of sensitization, and the distinct tendency for it to occur in families differentiate these individuals from the artificially sensitized, and suggest that there is some unknown factor here which is absent in men and animals subjected to artificial sensitization.

The introduction of foreign protein, however, results in essentially the same reaction in both instances and individuals in this state of spontaneous sensitization suffering from the effects of contact with protein ordinarily harmless must clearly be differentiated from the normal person who becomes ill from the absorption of one of the poisonous products which may through various means be split off from the protein molecule.

Undoubtedly certain violent intoxications in man are caused

[103] Gaz. d. hôp., 1912, lxxxv, 1969.

[104] Ztschr. f. Immunitätsf., orig., 1914, xxii, 641.

[105] Ibid., 1909–10, iv, 531.

[106] Since this lecture was delivered the important work of Cooke (Jour. Immun., 1916, i, 201) has been published. He has shown from a clinical study of the family history of a large group of patients suffering from such evidences of protein sensitization as hay fever and susceptibilities to certain foods, that sensitization affects members of families in a proportion which closely approximates the theoretical figures of the Mendelian law and suggests that sensitization is inherited in the strict sense and is transmitted as a dominant characteristic.

by the entrance into the body of these toxic products of protein digestion, and it is possible that they may give rise to symptoms which resemble the true anaphylactic shock. The rupture into the peritoneum of an echinococcus cyst is frequently attended by violent symptoms of collapse which Weinberg and Ciuca[107] have ascribed to anaphylactic shock. But as it is difficult to sensitize animals to the fluid of echinococcus cysts, or to show that animals or men carrying echinococcus cysts are sensitized to the fluid, and since the fluid itself is toxic, Graetz[108] concludes that the symptoms after rupture are not due to anaphylaxis but to the absorption from the peritoneum of toxic products split from the protein of the cyst.

The investigations of Whipple[109] and of Murphy and Brooks[110] upon the acute poisoning in dogs whose duodenum has been closed off in a loop, have shown that the symptoms are due to a toxin absorbed through the duodenal mucosa, and recently Whipple, Rodenbaugh, and Kilgore[111] have been able to isolate this toxin and show, as they believe, that it is proteose. It may be, therefore, that the acute collapse and toxic symptoms that accompany some of the severe gastro-intestinal disturbances are caused by the absorption of proteoses or such substances as histamin. These poisonous substances may be taken into the gastro-intestinal tract with the food, especially if it is spoiled, or they may be present there already. Such attacks of food poisoning are perfectly familiar, but it is questionable whether they result in sensitization, and they should not be confused with anaphylaxis.

So far our attention has been concentrated wholly upon the susceptibility of man to the proteins of animals and the higher plants or their split products, but it is necessary now to refer, at least briefly, to a somewhat different form of susceptibility but one of great importance, namely, "allergy" or changed reactivity or hypersusceptibility to infection.

The principle is beautifully illustrated by the classical experiments of von Pirquet on vaccination. Cutaneous inoculation of the normal individual by the virus of vaccinia results in the appearance after an interval of nine to twelve days of the typical skin lesion or local vaccinia, the normal reaction. Vaccination of a person recently immunized to cowpox shows within twenty-four hours the appearance of a small vesicle surrounded by a red areole which rapidly fades, and revaccination after several years results in a positive "take" which, however, appears early on the sixth or seventh day instead of the ninth or twelfth day as it does in the normal individual.

[107] Compt. rend. Soc. de biol., 1913, lxxiv, 1318; 1914, lxxvi, 340.
[108] Zeit. f. Immunitätsf., orig., 1912, xv, 60.
[109] Jour. Exp. Med., 1913, xvii, 286, 307; 1914, xix, 166.
[110] Arch. Int. Med., 1915, xv, 392.
[111] Jour. Exp. Med., 1916, xxiii, 123.

The similarity to the normal immediate and the accelerated reactions on inoculation and reinoculation of horse serum is very striking, and was immediately apparent to von Pirquet.

The relationship which anaphylaxis bears to this broad field of immunity and susceptibility, and the part which the poisonous products of protein digestion may have in causing the symptoms of infections, such as fever, was thoroughly discussed by Dr. Vaughan two years ago, and I shall therefore confine myself to one phase of the subject which will still repay study.

A method of studying the allergy to infection in man which has been developed within the last few years is the altered local reaction to the conjunctival, subcutaneous, or intracutaneous injection of bacteria or their extracts. The reaction of the conjunctiva and the skin of tuberculous patients to tuberculin is perfectly familiar. Similar specific reactions have been obtained with the extracts of bodies of the infecting bacteria in such disease as glanders, typhoid fever, syphilis, the trichophytic infections, and lobar pneumonia. In general it may be said that the response to the injection of these organisms or their extracts appears either during the course of the infection or after recovery of the individual. The tuberculin reaction, according to most observers, appears in animals fifteen to twenty days after infection by the tubercle bacillus. The typhoidin reaction of Gay can be obtained many years after recovery from typhoid fever. Müller, Gachtgens, and Aoki[112] who have studied the development of the mallein reaction in glanders in horses, state that the skin test may give a positive result on the fourth or fifth day after infection, and Weil,[113] who has recently described a cutaneous reaction obtained in a certain proportion of cases of pneumonia, when the autolysates of pneumococci are employed, states that the reaction first appears after the crisis.

The pathology of all these reactions is very similar, and though the histology of the lesion has only been studied extensively in tuberculosis, the few observations which have been made of the other reactions indicate that they resemble one another very closely, and consist principally in the infiltration of the subcutaneous tissues by mononuclear cells which are collected about bloodvessels. Unlike the reactions obtained with animal and vegetable proteins in sensitized individuals these reactions do not come on within the first few hours after inoculation, but make their appearance first in twenty to forty-eight hours. The tuberculin reaction may be delayed for two or three days and the luetin reaction for ten days to three weeks.

It is possible that similar local forms of allergy occur spontaneously during the course of many diseases. In the cases of chronic infections by the Streptococcus viridans the cutaneous hemorrhages

[112] Ztschr. f. Immunitätsf., orig., 1910, viii, 326.
[113] Jour. Exp. Med., 1916, xxiii, 11.

and painful nodules have been supposed to result from emboli to the skin, but Dr. Lamb, in studying a few of these lesions in serial section, has been unable to find thrombosed vessels. The histological picture is again not unlike that seen in the tuberculin reaction. Quite similar is the change in the glomeruli of the kidney so common in these cases and so unlike the acute suppurative processes usually encountered in acute infections, that it is possible it may represent an allergic reaction toward the infecting organism.

Faber[114] has recently shown that a previous injection of streptococci into the joint of a rabbit will alter the local resistance of the joint in such a way that intravenous injections of that type of streptococci which in normal animals rarely, if ever, affects the joints, invariably produces in the treated animals a localized infection of the joints in these animals. This local allergy seems, too, to be specific. Finally, one may cite the transition of an acute local infection to a chronic local inflammation as a beautiful example of allergy or changed reactivity to an infecting organism. It is worthy of notice, too, that many of these local allergic processes are associated in human beings with the appearance of mononuclear cells. In rabbits the polymorphonuclear leukocytes predominate both in the tuberculin reaction and in that obtained with animal proteins.

During the artificial immunization of both man and animal by repeated subcutaneous injections of bacteria or their extracts both local and general reactions occur which must be interpreted as an evidence of allergy. It is generally recognized that severe local and general reactions are much more likely to occur in patients who have had typhoid fever or who have been subjected to previous inoculation than in normal individuals, and that the local or general reaction in normal persons is more likely to be severe following the second or third inoculation than after the first. Nichols[115] states that severe local reaction occurs in 50 per cent. of cases after repeated inoculation. In very rare instances the general reactions following large injections of bacterial vaccines spaced at long intervals are immediately followed by alarming collapse, swelling of the face, dyspnea, and suppression of urine a condition not unlike anaphylactic shock.

Indeed many of these condition have been ascribed to sensitization, likened to anaphylaxis and accepted as such. Bacterial bodies contain nucleoproteins, the proportion of nitrogen varying in different bacteria from 8 to 10 per cent., and it cannot be doubted that it is possible to produce anaphylaxis with bacteria or their products though the primary toxicity of these suspensions and extracts is often so great that the results of many experimenters leaves one in doubt as to whether the effect of injection is really

[114] Jour. Exp. Med., 1915, xxii, 615. [115] Ibid., 780.

that of anaphylactic shock or some other form of rapid intoxication. In working with bacteria the results are always complicated by the presence of poisonous substances, whatever their origin, and until it is possible to obtain from bacterial bodies proteins free from the toxic split products, or substances developed from bacterial growth, it will be difficult to determine what part the true protein sensitization and the anaphylactic reaction plays in susceptibility and infection.

Even the extensive studies upon tuberculosis have not completely explained the reactions which Koch's O. T. tuberculin, which is a glycerin broth filtrate, calls forth. In general the reactions produced in the tuberculous individual differ very slightly from those obtained with bacillus emulsion or extracts rich in protein, but with the latter animals may be readily sensitized, while with the former, though such sensitization has been accomplished, it is with great difficulty, and the reactions according to Lewis[116] are dependent upon the protein in the broth rather than in the extract from the bacilli. Though Baldwin[117] showed that animals may be sensitized with tuberculoprotein as with other bacterial proteins, most workers have failed to sensitize guinea-pigs passively with the serum of tuberculous patients or animals. Austrian[118] has shown that such a thing is possible if tuberculoprotein instead of Koch's O. T. tuberculin is used as antigen. Animals actively sensitized to tuberculoprotein may give a very faint skin reaction to O. T. tuberculin, though the infected animals, of course, react strongly. In fine, the skin reaction and the general reaction to O. T. tuberculin seem to depend upon the presence in the body of an active tuberculous focus, and Bail[119] in transplanting tuberculous tissue from a tuberculous to a normal animal found that the reaction after the injection of tuberculin always takes place in the tuberculous tissue. It is evident, therefore, that though the reaction in the tuberculous patient or animal is the same whether tuberculoprotein or O. T. tuberculin is employed, the anaphylactic reactions differ greatly and cannot be obtained with the latter.

To what extent the forms of allergy, such as the diagnostic skin reaction, in other infectious processes are dependent upon protein sensitization, and can thus be accredited to true anaphylaxis, is uncertain, but before sweeping conclusions can be made upon the identity of allergy and anaphylaxis much careful experimental work is necessary.

The analogy is very close, however, and since one of the striking features in infectious processes is the response on the part of the body by exudation and proliferation of cells, namely, an inflamma-

[116] Arch. Int. Med., 1909, iv, 528.
[117] Jour. Med. Research, 1910, xxiii, 189.
[118] Jour. Exp. Med., 1912, xx, 149. Bull. Johns Hopkins Hospital, 1913, xxiv, 280.
[119] Ztschr. f. Immunitätsf., orig., 1911–12, xii, 451.

tion, it is important to determine whether similar processes accompany or follow anaphylactic reaction to simple proteins. The characteristic result of acute shock in guinea-pigs is the appearance of hemorrhages. But the guinea-pig that has recovered from a single shock shows no permanent trace of these lesions. Repeated injections of serum made subcutaneously in rabbits, on the other hand, give rise to edema, hemorrhage, and necrosis, as was pointed out by Arthus, and the lesion is characterized according to Schlecht and Schwenke[120] by an exudation of mononuclear cells and eosinophilic leukocytes. Friedberger and Mita[121] and Ishioka[122] showed, too, that horse serum sprayed into the trachea of sensitized guinea-pigs produced a cellular type of pneumonia, the exudate into the alveoli being rich in mononuclear cells and eosinophiles. We[123] have found that repeated intravenous injections of horse serum and egg-white in sensitized guinea-pigs, rabbits, dogs, and cats brought about focal necroses in the liver, kidney, and heart muscle which was followed by an exudation of mononuclear cells. In over 80 per cent. of the animals changes were found in the kidneys which were often so extensive that they led to an advanced form of nephritis.

Though it would not be justifiable to apply the results of such experiments to disease in man, it is interesting to note that one of our patients who showed spontaneous sensitiveness to several proteins from plants, and especially to phaseolin, and who had had several violent attacks of asthma, urticaria, and diarrhea after eating beans, developed a pronounced and persistent albuminuria and cylindruria following such an attack one year ago. Undoubtedly infection is the most important factor in the cause of nephritis in men, but such observations suggest that the progressive process in the kidney may depend upon an allergy or altered susceptibility of this tissue towards the bacterial proteins.

It is known that about 10 per cent. of patients with serum sickness have a mild degree of albuminuria and show both hyaline and granular casts in the urine, and it was, therefore, with much interest that Dr. Rackemann and I studied the functional activity of the kidney during the course of this disease. Most of the patients have developed their serum sickness after the use of large amounts of antipneumococcus serum, which Dr. Cole has kindly furnished us for the treatment of pneumonia caused by the pneumococcus type I. In this study attention has been paid especially to the excretion of phenolsulphonephthalein, water, and sodium chloride. The nitrogen metabolism is so much disturbed during and after an

[120] Deut. Arch. f. klin. Med., 1912, cviii, 405.
[121] Deutsch. Med. Wchnschr., 1911, xxxvii, 481.
[122] Deutsch. Arch. f. klin. Med., 1912, cvii, 500.
[123] Jour. Exp. Med., 1913, xviii, 678; 1915, xxii, 793. Arch. Int. med., 1915, xv, 1079.

attack of pneumonia that little significance can be attached to the changes in the total non-protein nitrogen of the blood. The coefficient of urea excretion, however, employed by Ambard has been studied by the recent modification in technic described by McLean,[124] and we have not found that this is greatly modified during serum sickness. The excretion of chlorides and water, on the other hand, is often profoundly affected. The changes that take place in the elimination of salt and water during convalescence from an attack of pneumonia, that has not had serum are as follows: During the attack the excretion of water is low and the chlorides are eliminated in small amounts and low concentration. Shortly after the attack the retained chlorides are excreted in excess of the intake and in high concentrations, but on a fixed water and salt intake soon come to a normal balance. We have not found that this course is materially interfered with by such febrile complications as empyema. In the serum sickness that may follow the use of antipneumococcus serum, and in one case after the intraspinous injection of antimeningococcus serum, the ordinary course of the elimination of water and sodium chloride is greatly disturbed. With the onset of serum disease the excretion of water diminishes rapidly and with it the elimination of sodium chloride. One important point, too, is that the patient is unable to concentrate the sodium chloride, which may fall below 0.2 per cent., a very low figure. The excretion of phthalein is in a few cases slightly affected as well, and with the appearance of albumin and casts in the urine and the development of edema, the patient present a clinical picture very closely resembling a mild case of nephritis, of the salt retention type. Sufficient studies have not been made to determine whether this salt retention is in the blood or tissues, but at all events it is usually accompanied by edema. These alterations, so far as we have observed them, are purely transitory and with the subsidence of the attack the patient and the renal function return to a normal state.

Such studies are designed primarily to throw some light upon the possible importance of repeated anaphylactic shocks in the spontaneously and highly sensitized individual, and it would be the greatest mistake and misfortune at the present time if they were allowed to have any bearing on the use of antitoxic and antibacterial sera. The concentrated diphtheria antitoxin, such as is employed, now rarely produces serum disease or sensitizes sufficiently highly to make a second dose, particularly if it is given subcutaneously, in the least dangerous, and it is only to the spontaneously sensitive who react to the first injection that harm is likely to come.

To prevent accidents in such unexpected instances, especially if large quantities of serum are given intravenously, a preliminary intracutaneous injection of 0.1 to 0.01 c.c. of serum should be made

[124] Jour. Exp. Med., 1915, xxii, 212.

to determine whether or not the patient is spontaneously sensitive to the serum which is to be employed.

Though it would be interesting to recount the methods which have been employed to desensitize both artificially and spontaneously sensitized individuals, this important problem in therapeutics must be left, since there is no time to do it justice, and in conclusion I shall point out the conditions which such methods must combat.

The injection of foreign proteins in man brings about the same condition of hypersensitiveness toward subsequent injections that it does in animals.

Certain individuals may show spontaneous hypersusceptibility to one of several foreign proteins. That these people differ from the artificially sensitized, in that their susceptibility is very great, is shown toward several different proteins, and has a tendency to occur in families. And, finally, that this state is associated with and directly responsible for some well-defined pathological conditions.

THE SYMPTOMS AND PHYSICAL SIGNS RESULTING FROM WOUNDS OF THE CHEST.[1]

By C. P. Howard, M.D.,
IOWA CITY, IOWA.

From August 7 to November 1, 1915, there were admitted 3039 to the hospital to which the writer was attached; of these 1315 were sick and 1724 wounded; of the latter, 107 (6 per cent.) received either a gunshot wound or shell wound of the thorax; 20 cases were evacuated too rapidly to permit of a physical examination of the chest. This leaves 87 cases for purposes of analysis.

Forty-five were the result of gunshot wounds, and of these 41 penetrated the thoracic cavity; the remaining 4 were merely wounds of the parietal wall without obvious penetration of the pleural cavity.

Forty-two were the result of shell wounds of some kind, as high explosive, shrapnel, trench mortar, or hand grenades. Of these, 28 had certainly penetrated the chest wall and 14 had apparently not, though 1 at least had caused a fracture of a rib which had lacerated the pleural cavity.

These cases we shall divide into four groups for purposes of description and consideration.

[1] I wish to express my appreciation to Col. Birkett, Lt. Cols. Elder and McCrae, Majors Hill and Archibald and the other officers of No. 3, Canadian General Hospital, for the opportunity to see the cases and for permission to publish them.

GROUP 1. Fifteen patients presented no abnormality in the lungs or pleuræ at the time of the examination. That is to say, 17.2 per cent. of wounds of the chest revealed no injury to lung or pleura a few days after the receipt of the injury, and that in spite of the fact that of these 6 were penetrating gunshot wounds and 1 penetrating shell wound. The remaining 8 had only affected the parietal wall.

GROUP II. A very interesting group of 6 cases comprised 4 cases of pneumonia and 2 of serous pleurisy with effusion. The 4 pneumonias all resulted from shrapnel, 2 of which were penetrating wounds. Further, what was of special interest in 2 cases, the involvement was on the side opposite to the wound. A third case was a double pneumonia associated with paralysis of the vocal cord from a missile lodging in the upper right chest behind the first rib, and was possibly originally an aspiration pneumonia. The fourth pneumonia patient had only a small shrapnel wound of the thorax, but was buried in a trench for some time and consequently much bruised about the thorax. One of the pleurisy, with effusion, cases had an accompanying pneumonic consolidation of the lung resulting from a non-penetrating gunshot wound of the opposite side. The other case was a simple serous effusion the result of a non-penetrating shell wound of the same side.

GROUP III. This includes one case of mediastinitis, resulting from a rifle bullet lodging in the anterior mediastinum. The only symptoms complained of were pain referred to the right side of the neck over the upper and outer border of the trapezius muscle and slight dysphagia. On inspection there was a marked area of ecchymosis over the manubrium, but, of course, as yet, no fulness of the superficial veins. There was in addition a non-fluctuating elevated tender area beneath the discolored skin from the subcutaneous hemorrhage. There was a definite area of dulness corresponding to the anterior mediastinum, reaching above to the upper margin of the manubrium; below merging with the heart dulness, extending to the right about 1 cm. beyond the sternal border and to the left just to the sternal border. On auscultation over the manubrium and raising the patient's arms above his head there was a well-marked grating friction, a sign described by Perez[2] and reported by the writer[3] in other cases of mediastinitis. A skiagram revealed a sharply pointed bullet slightly more than one inch in length lying apex downward behind the manubrium to the right of the midline one inch from the surface.

GROUP IV. This group comprises the hemothorax cases which for purposes of discussion have been further subdivided into the infected and sterile.

[2] Brit. Med. Jour., 1896, i, 82.
[3] C. P. Howard, Johns Hopkins Hosp. Bull., 1915, xxvi, 140.

A. *Infected Hemothorax.* Of the 65 cases, 9 were definitely infected (13.8 per cent.). This is a somewhat lower percentage than that given by Col. Sir John Rose Bradford[4] in his series in which 25 per cent. of 328 cases were infected. Hale White[5] found only 10 per cent. of the cases in his base-hospital experience in England with evidence of infection of the fluid.

As to the nature of the wounds, 4 were penetrating gunshot wounds, 4 were penetrating shell wounds, and 1 was a non-penetrating shell wound which had caused a fractured rib, a spicule of which had lacerated the pleura and was to all intents and purposes a penetrating chest wound. The infective organism was one of the gas bacillus group in 1 case, B. tetani 1 case, pneumoccus 1 case, streptococcus 1 case, Streptococcus and Staphylococcus aureus one case, and a large unidentified bacillus (recovered on three separate aspirations) 1 case. In the remaining 3 no cultures were made.

Cough, hemoptysis, pain, and dyspnea were present in about the same proportion as in the next group, under which these symptoms will be discussed in detail.

As one might expect, the temperature range was higher in this group than in the non-infected cases, and not uncommonly ran a more or less continuous curve of 103° to 104° F. This fever curve taken in conjunction with the rapid pulse (120 to 140) and a marked tendency to polypnea (28 to 40) would always suggest the chart of ordinary acute lobar pneumonia.

In 2 cases the infection lay dormant for ten days and eighteen days respectively. In the first of these cases a penetrating shrapnel wound was received on September 25; an exploratory aspiration on October 1 revealed a bloody fluid, smears and cultures from which were negative for organisms; a second aspiration on October 5 revealed a number of organisms of the "gas-bacillus group;" a third aspiration on October 7 showed the same organism, though in smaller numbers. The second case received a penetrating gunshot wound on October 13 and ran a normal temperature, pulse, and temperature curve until October 31, when there was a sudden rise in all three (temperature, 104.4°; pulse, 120; respiration, 28), and an exploratory puncture revealed a large bacillus morphologically resembling one of the gas bacillus group, but which grew aërobically as well as anaërobically, did not produce gas, and was unidentified, but probably belonged to the group of diphtheroids found by others in this war; that it was the cause of the infection of the pleural exudate cannot be doubted, as it was found alone on three separate aspirations.

Physical Signs: The physical signs in this group differed in no way from those of the sterile cases. We never found the two signs

[4] Brit. Jour. Surg., 1915, iii, 247.

[5] Lancet, 1915, ii, 1233.

of anaërobic bacillus infection described by Bradford, namely, a rapid displacement of the heart and a "cracked-pot" percussion note from the rapid development of gas within the pleura.

Only 2 of the cases showed definite signs of pneumothorax, while in a third air and pus could be seen and heard sucking in and out of a large wound in the upper back, though none of the characteristic signs of pneumothorax could be detected, but merely those of an extensive fluid exudate. This case interested me much at the time. West[6] reports 2 cases with large wounds of the chest in which the lung did not collapse, though no adhesions were present, and in which there were no signs of pneumothorax. All of us have noted the absence of signs of pneumothorax after thoracotomy for a recent empyema. On the other hand if the empyema be of long standing and firm adhesions have formed, causing pocketing of air and pus, well-marked signs of pneumothorax may be present, as in a case seen recently in the surgical clinic (University Hospital, No. 2609). While infection should be suspected in every case which is not progressing favorably after the fourth day, it cannot be diagnosed on clinical symptoms and signs alone. An exploratory aspiration and a bacteriological examination (both smears and cultures) should be made in all suspicious cases.

As regards treatment, in 4 of the cases a thoracotomy was done, as a result of which 2 were discharged well, 1 improved, and 1 died. One case which was drained at a casualty clearing station by inserting two rubber drainage tubes between the eighth and ninth ribs in the posterior axillary line, died five days later under our care. One case was merely aspirated and was discharged improved, but whether or not he subsequently required more radical treatment is not known. In 3 cases no surgical procedures were instituted: in 1 case because a coexisting tetanus caused death; in 1 case because the patient was moribund upon admission; the third was evacuated to England at the patient's request in an apparently hopeless condition, owing to the existence of a complete paraplegia of the lower extremities

One striking feature of the cases in which a thoracotomy was performed was, in spite of the promptness of the surgical interference, the slowness of the convalescence owing to the marked tendency in these cases to the formation of adhesions and the consequent pocketing of pus that occurred.

B. *Sterile Hemothorax.* This was by far the largest group, comprising as it did 56 patients. Thirty-one were the result of gunshot wounds, of which all but one had penetrated the chest cavity. In 25 shrapnel, hand grenades, or some form of shell was the cause of the wound, 20 of which had obviously penetrated the thoracic cavity; in the remaining 5 no penetration wound was

[6] Emerson, Johns Hopkins Hosp. Reports: 1913, xi, 375.

demonstrable, and the hemorrhage must have resulted from laceration of the intercostal arteries or severe contusion of the lung itself.

The four chief symptoms were cough, hemoptysis, dyspnea, and pain in the chest.

Cough was a most constant symptom, being present in 41 cases, absent in 9, and not noted in 6. In other words, it was present in 82 per cent. of cases in which a definite note was made. For the most part it was the characteristic short, sharp, dry cough of an ordinary pleurisy. Apart from these cases, in which a definite hemoptysis occurred, sputum was strikingly absent

Hemoptysis was also a very constant symptom, being present in 39 cases, absent in 7, and not noted in 10. In other words, in 85 per cent. of the cases blood was expectorated. This varied from a few mouthfuls immediately after the reception of the wound to a more prolonged and repeated hemoptysis persisting in some cases for days. Of course, in the immediately fatal cases which were not seen by us very extensive external hemorrhage must occur in many cases. While hemoptysis is usually due to penetration of the lung, with laceration of a bloodvessel, Rose Bradford[7] believes it might also be due to an infarction of the lung from bruising when there is no proof that the missile had penetrated the lung substance. A fatal hemoptysis occurred only once in 1000 cases studied by this author.

Dyspnea was a somewhat less frequent symptom, occurring in 21, absent in 10 and not noted in 25. That is to say, it was present in approximately 70 per cent. of the cases. It was rarely marked and usually of short duration; even the cases with a small pneumothorax showed at the most slight respiratory embarrassment.

Pain in the chest was present in 24 cases, absent in 7, and not noted in 25. This means approximately 80 per cent. of the patients with a complete history complained of pain somewhere in the chest, usually at the site of the wound, though not infrequently in the axilla or front of the chest. It was always worse on breathing or on movement of any kind.

Fever of varying degree was noted in 47 patients, and was absent in 9 (*i. e.*, 99° or less). That is, 92 per cent. showed fever. Of these 20 patients had a temperature at one time or another of 102° F. or over, and 3 even of 104°. Another 12 had a rise to a point between 100.2° and 101.8°; and 15 between 99.2° and 99.8°. The presence of fever by no means indicated an infection of the pleura or underlying lung, and was due in these cases either to an infection of the parietes or to absorption of the blood contained in the pleural cavity, the latter being analogous to the so-called protein fever of the experimental laboratory.

[7] Brit. Med. Jour., 1916, i, 129.

The pulse was accelerated in every one of the 56 cases (100 per cent.). In 10 cases it was markedly (120 or more per minute), in 35 moderately (90 to 119 per minute), and in 11 slightly elevated (80 to 89 per minute). This was no doubt due in part to the parietal infection, but chiefly to the physical exhaustion and shock experienced by the patient, as the pulse rapidly returned to normal after proper rest in bed and suitable nourishment. Hemorrhage itself played but a small role, and that only in a small proportion of cases.

Respirations were about normal in 43 of 54 cases (80 per cent.). They were markedly accelerated (*i. e.*, 32 or more per minute) in 12, moderately (25 to 30 per minute) in 14, and slightly (22 to 24 per minute) in 17 patients. In 13 cases the respiratory rate was normal upon coming under our observation at the base.

The physical signs were as follows: *Inspection* yielded invariably a diminished movement of the affected side; in some cases this was exaggerated by the patient's apprehension of causing pain or producing a hemorrhage. Fulness was not a constant feature except in the very extensive effusions. Two or more weeks after the wound one was not infrequently struck with the subsequent retraction of the thoracic wall more than one sees in civil life, except in cases of empyema or fibroid phthisis. This was due to the marked collapse of the lung, and according to writers in England is entirely recovered from as the lung expands from suitable exercises.

Palpation frequently reveals the characteristic crackling of subcutaneous emphysema for a considerable distance around the wound, being present in 10 of our 56 cases. This phenomenon no doubt is due to escape of air from the underlying lung, and is subsequent to a transient pneumothorax, though in only 2 of these cases were the other physical signs of air in the chest present. Of course, the diminished motion could also be detected. Tactile fremitus was diminished in the great majority of cases (90 per cent.), and in the remainder it was either normal (1 case), increased (1 case), or diminished in front and increased behind (2 cases). Increase of vocal fremitus is readily explainable by the compression of the underlying lung, and in our series, considering the other evidence of compression, was surprisingly rare.

Percussion. The note was usually dull in moderate effusions (30 cases) and of a woodeny flatness in the larger effusions (18 cases); in 8 no remark as to the quantity of the effusion was made. A tympanitic note was present in front or above the line of effusion in 4 uncomplicated cases, and was no doubt the Skodaic hyperresonance present in simple effusions above the level of fluid. In 3 other cases, however, the tympany was associated with other suspicious signs of a pneumothorax. In 8 additional cases the tympany occurred in conjunction with other more definite signs of a pneumothorax.

Rose Bradford called our attention to the frequency of an atonic relaxation of the diaphragm, so that the area of gastric tympany was found to extend unusually high on the left side; this phenomenon he does not believe to be due simply to a wound of the lung, for it only appears with hemothorax.[8] We examined for it in too few cases to express an opinion as to its value.

Auscultation. The breath sounds were, for the most part, suppressed or absent (30 cases), but in 19 other cases (39 per cent.) they were noted as bronchial over the back or above the line of effusion. This again shows the frequency and extent of compression of the lung. In 7 cases no note was made as to the character of the breath sounds. The vocal resonance, as determined by the transmission of the spoken voice sound with the aid of the stethoscope, was increased in 11 cases, diminished in 12, and normal in 1 case. In the remainder no note was made. Here again we find evidence of the frequency of compression of the lung.

The transmission of the whispered voice sounds (pectoriloquy) was only tested for in 5 cases, but was present in 4 of these.

Medium or fine moist rales were noted only seven times in spite of the frequency of compression of the lung. A pleural friction was more frequent, being present in 12 cases, in 3 of which it had the pleuropericardial character.

There were 8 cases of undoubted pneumothorax and 5 suspicious cases, and yet a metallic tinkle was heard in only 6 cases and the coin sound or "bruit d'airain" of Trousseau in 4. The Hippocratic succussion was not tested for, owing to the importance of keeping the patients as quiet as possible.

Cardiac displacement was a very constant sign, being present in 23 cases of 32 (72 per cent.) in which a note was made as to the position of the heart. We were much struck with the degree of displacement even when the effusion was relatively small in amount, and considered it to be further evidence of the probable frequency of the existence of a pneumothorax in the early stages of the thoracic injury. The greater density of the fluid as compared with that of ordinary serous effusions did not satisfactorily explain the greater displacement of the heart in these cases. The heart very slowly returned to its normal site even after the effusion had largely subsided, and in many cases the patient was sent to England with considerable cardiac displacement persisting.

Roentgen-ray Findings. In only 20 cases was a skiagram taken, first, as in the cases with a wound of exit it was unnecessary, and secondly, as we moved our patients as little as possible. In 12 of these cases the missile was located in the thorax, in 1 case it had penetrated the diaphragm, and had come to rest in the abdominal cavity. In the other 7 cases no foreign body could be found. In

[8] J. Rose Bradford and T. R. Elliott, Brit. Jour. Surg., 1915, iii, 247.

3 cases fluid was still present when a search was made for the foreign body. In one other case a pneumothorax still existed.

Complications. In 2 cases there were undoubted signs of fluid on the two sides of the chest, and in a third there were signs of either a small effusion or a marked displacement of the posterior mediastinum and its contents.

As was noted before there were 8 cases of undoubted *pneumothorax* and 5 in which there was more than a strong suspicion. The majority of these cases were admitted within a day or two of one another after the British offensive of September 25 and 26, 1915, when the wounded were evacuated very rapidly to the base. Further, the signs of air in the chest rapidly disappeared, in several instances in twenty-four hours. The greater incidence in those seen shortly after being wounded and the rapid absorption of the air under observation lead us to believe, with all due respect to the opinion of Sir John Rose Bradford,[9] that a mild form of pneumothorax is a common occurrence and must be present in the majority of cases in which a missile has penetrated the lung. It is of interest to know that Otis[10] noted in the American Civil War not more than 6 cases in which a pneumothorax was a troublesome complication. We must admit with Rose Bradford that over an area of cutaneous emphysema the character of the percussion note may suggest the presence of a pneumothorax when none is present. Rose Bradford found only 12 cases of pneumothorax in 500 patients with wounds of the chest, and in only 5 was its presence proved. Hale White found only 2 cases of air in the pleural cavity in the 50 cases seen by him in England. Naturally the amount of air that escapes is very small if the missile be a high velocity bullet from a rifle or machine gun, and consequently is overlooked unless carefully examined for within forty-eight hours or so after the reception of the wound. Further, of course, there is seldom if ever a valvular opening such as one sees in a pneumothorax due to tuberculosis. As shown in several autopsies of the infected hemothorax group there is at once a sealing of the opening in the lung substance by fibrin, which effectually prevents further escape of air. In 1 case the fibrinous plug had been inflated like a small balloon by the air in its attempt to escape from the damaged lung. Lastly, Osler,[11] has pointed out that the metallic phenomena which are the most striking signs of air in the chest, are best heard in cases with a consolidated lung and thickened pleura. Distention, immobility, lack of vocal fremitus, hyperresonance, absence of breath sounds and displacement of viscera are the signs of a pure pneumothorax, and can readily be confounded with those signs of an extensive effusion.

[9] Loc. cit.
[10] Med. and Surg. Hist. of War of Rebellion, Pt. I, vol. ii, 623.
[11] Practice of Medicine: 8th edition, 1912, 671.

Lobar pneumonia was present in 4 cases, all four being on the side opposite to the wound and the subsequent hemothorax. These 4 cases together with the two mentioned in Group II give a total of 6 cases in our series in which all the physical signs and symptoms of a pneumonic infection existed in the side opposite to the injury. While trauma is a well-recognized cause of pneumonia since the days of Litten, who found a history of it in 4.45 per cent., I can find no mention in the current text-books and monographs of the opposite lung being involved. It is difficult to understand the pathogenesis of a pneumonia by "contre-coup." Rose Bradford noted that the hemothorax and pneumothorax might be found in the side opposite to the wound in the chest when the bullet penetrated the lung transversely. He noted that contralateral pleurisy was commoner in the cases infected with streptococci; he further admits that pneumonic consolidation does occasionally occur in the contralateral lung[12] but never in the side of the hemothorax.

A secondary hemorrhage into the pleural cavity is an exceedingly rare event if the patient be kept completely at rest for several days after his injury. In some cases it is said to have been the cause of death when attempting to transport the patient to the base too early. In 100 autopsies reported by Henry[13] death was due to hemorrhage in only 8.

Private D. J. B., Reg. No. 16691, was admitted to our care forty-eight hours after receiving a shrapnel wound of the right chest in the third interspace anteriorly. On admission, in addition to signs of a moderate hemothorax, there were undoubted evidences of pneumothorax; four days later, during which time he had been kept strictly at rest, he became extremely pale, the pulse became very rapid and thready, and the respiration became more rapid and labored. The diagnosis lay between a virulent infection of the hemothorax, as described by us above, or a secondary hemorrhage. The whole picture was more suggestive of the latter. However, to make certain, an exploratory needle was introduced and a few cubic centimeters of blood which clotted in the syringe were removed. That the blood was clotted was proof of the recent occurrence of the hemorrhage, as the bloody exudate usually removed by aspiration or drainage shows little or no clotting *in vitro*. Further the smears and cultures were negative and the patient gradually recovered with merely supportive treatment and absolute rest.

A case of cholohemothorax has been reported by Elliott and Henry[14] from a fistula between the liver and pleura following a bullet wound.

In 3 cases there was a simple fibrinous *pericarditis*, as evidenced by the presence of a pericardial friction. In 2 of these cases the wound was in the left chest. In another patient who had received

[12] J. Rose Bradford and T. R. Elliott, Brit. Jour. Surg., 1915, iii, 247.
[13] Brit. Med. Jour., 1915, ii, 130.
[14] Ibid., 1916, i, 9.

a gunshot wound of the chest, the bullet having entered at the left nipple and passed out at the right nipple, there were signs of fluid (namely, a triangular area of absolute cardiac dulness and distant heart sounds), with the subsequent development of a to-and-fro pericardial friction, all of which were very suggestive of a hemopericardium.

In still another case there were the characteristic signs of a *pneumopericardium*. As I hope to report the case at some length in the near future, suffice it to say that the patient received a shell wound of the lower left posterior aspect of the chest; the missile must have penetrated the diaphragm as well as the pleura, with the production of a subdiaphragmatic abscess. Two weeks after the receipt of the wound he developed sudden dyspnea, rapid pulse, precordial tympany, absence of heart sounds, and the presence of a most remarkable to-and-fro churning, musical, echoing sound synchronous with the systole and diastole of the heart, and persisting upon holding the breath. Some days later, after the air was absorbed, a dry pericardial rub became audible.

Twelve cases were complicated by extensive *infection* of the tissues from wounds for the most part other than those about the chest. In 2 cases the patient nearly succumbed to a secondary hemorrhage from the invasion of one of the main arteries of the upper or lower extremity. The case of the subdiaphragmatic abscess has already been referred to.

TREATMENT. In the majority (70 per cent.) of the cases apart from absolute bed rest and a bland nutritious diet no treatment was necessary, the bloody exudate being absorbed usually at the end of fourteen days after the reception of the wound. In 3 cases, in spite of the presence of signs at the expiration of two weeks, an exploratory aspiration was negative. In 5 other cases an exploratory aspiration revealed sterile bloody fluid, but the withdrawal of a few cubic centimeters sufficed to promote absorption. In another 5 cases amounts varying from 400 to 1600 c.c. were removed. This fluid was withdrawn slowly by means of an ordinary Potain aspirator without causing any outward symptoms. It never reaccumulated. The fluid itself varied in color from an ordinary deep scarlet to a deep chocolate; it was usually thin but sometimes of a syrupy consistence, and on standing showed little or no clotting. Only in one instance was an appreciable amount of fibrin noted. The postmortem examination of one case in the setrile and in several of the infected cases readily explains the absence of clotting *in vitro*, as the visceral and parietal pleuræ were covered by thick fibrin which had evidently separated out *in vivo*. This fibrin not infrequently plugs the lumen of the needle unless a large one (preferably a trocar) be used. Upon standing a sediment of red cells in various stages of decomposition with an occasional leukocyte can be found.

Henry[15] believes that primary coagulation of the effused blood and a deposition of fibrin occur in a few hours; afterward exudation of lymph may occur which will induce secondary clotting. Denny and Minot[16] offer experimental proof that the blood remains fluid in the pleural cavity not because of any alteration of its elements but because of previous coagulation and defibrination. Following the suggestion of Colonel Sir John Rose Bradford, two cases of extensive simple hemothorax were treated by aspiration and oxygen replacement. We used a simple home-made manometer and the oxygen tank of the Clarke oxygen-ether apparatus, introducing two needles into the chest, one for aspiration and one for the oxygen to enter. An attempt was made to keep a constant pressure equal to that noted before the withdrawal of any fluid. Of course, the resultant pneumothorax persisted for two or three days, and then gradually disappeared. We see no reason why all cases could not be aspirated if this procedure be used early (let us say on the sixth or seventh day) without giving rise to secondary hemorrhage, as was experienced by the physicians of the Royal Army Medical Corps in the South African War.

Prognosis. Of the 87 cases only 6 died (69 per cent.), and of these 6 cases 4 were infected hemothorax, 1 died as the result of multiple amebic abscesses of the liver with local peritonitis, and 1 from an infected bullet tract in the lung. That is to say, approximately 8 per cent. of our hemothorax series died, which approximates very closely the mortality of Rose Bradford's series. In the latter's series of about 450 cases 10 per cent. died from sepsis, 5 per cent. from hemorrhage, and others from sundry complications.

In our series 69 were discharged well (79.3 per cent.), 11 improved (12.6 per cent) and on the high road to recovery; 1 was sent to England unimproved because of a coexisting paraplegia of the lower extremities. These encouraging figures, of course, hold true for only those cases which are removed from the battle-field and are eventually evacuated to the base. Many wounds of the chest must be fatal within a short time. As to what is the proportion of these we have as yet no figures to guide us. The ultimate prognosis of wounds of the chest, according to Hale White, seems to be good, for it is not uncommon to see such cases returned to the firing line. Convalescence is necessarily slow, but the flattening of the chest almost disappears in the course of several months.

[15] Loc. cit.
[16] Amer. Jour. Physiol., 1916, xxxix, No. 4.

SPECIFIC AND OTHER FORMS OF SPONDYLITIS.

By B. Sachs, M.D.,
NEW YORK.

(From the Neurological Service of Mt. Sinai Hospital.)

Some early forms of spondylitis constitute a No Man's Land, definitely charted by none, and vaguely claimed by all. The chronic cases belong very properly in the domain of orthopedic surgery. The incipient and more acute forms are recognized more readily by the neurologist. Traumatic spondylitis, tuberculous spondylitis, as well as those forms of carcinomatous or sarcomatous deposits in or near the vertebræ are not to be considered in this discussion.[1] Special attention is to be directed to specific spondylitis and to a senile form, which, for want of a better term, may be designated as a chronic or universal spondylitis closely allied to spondylitis deformans. I wish also to direct attention to that form of spondylitis occurring in the senile period which has been the subject of considerable study.

In the neurological division of Mt. Sinai Hospital the question of spondylitis has arisen so frequently within the last few years that a thorough examination of the spinal column has become a matter of routine. Our own experience has been opposed to that of Nonne, Oppenheim, and Lewandowski, who regard specific spondylitis as a relatively rare disease.

In his well-known monograph Nonne states that Eugene Frenkel did not discover a single case of unquestionable luetic caries during a period of thirty years as pathologist of the large hospitals of Hamburg. Leyden and Jurioux were of the opinion that a mistaken diagnosis might be made if we considered every case of caries in a specific subject necessarily syphilitic. Nonne refers to a patient who exhibited the symptoms of cervical caries one year after a specific infection. The patient died seven years later of a general tuberculosis. At the autopsy he found a tuberculous caries associated with a specific meningitis. We are all fully aware that the histological differentiation between tuberculous and syphilitic tissues is a difficult matter, and even with our present modern methods, especially with the aid given us by roentgen-ray examinations, the question cannot in every case be settled satisfactorily as to whether a given lesion be tuberculous or specific, and yet in a vast majority of the cases there are sufficient points of differentiation, some of which are brought out by a careful study of the roentgen-ray findings.

[1] Held before the New York Neurological Society at its meeting December 7, 1915. The subject was illustrated by lantern slides and radiographic demonstrations.

Whatever the etiological factor may be the clinical symptoms are about as follows: First of all, a partial or complete immobility of some part or parts of the spinal column. In the cervical cases there is distinct rigidity of the neck and almost complete fixation of the head. In many instances there is distinct pain on pressure over the spinous processes. Among the other symptoms, in the order of their importance, we may rank radiating pains, according to the segments involved, typically root pains; slight atrophies of the muscles around the neck and shoulder girdle or of the hip and thigh muscles. There are distinct areas of altered sensibility varying from slight anesthesias to distinct hyperalgesias of the sort that we are accustomed to encounter in cases of spinal neoplasm, and for this reason, as well as for the painfulness on pressure, the differential diagnosis between spondylitis and neoplasm of the cord is to be considered. Wasting of the muscles, a paretic condition of the affected parts, and altered reflexes, either diminished, if due to involvement of the roots, or increased reflexes, associated possibly with spastic forms of palsy if the spinal cord is at all compressed, constitute a striking clinical picture.

These symptoms may, of course, be aggravated to such an extent that the patient finally presents all the symptoms of a compression myelitis. The variability of the symptoms, the exacerbation and remission, and, finally, the prompt subsidence in accord with therapeutic measures are so characteristic of all syphilitic lesions that they help to suggest the special character of these luetic forms. The suspicion of the syphilitic origin of these forms of spondylitis is confirmed by the Wassermann reaction of the blood and possibly of the spinal fluid as well as by the increased lymphocytosis and the high cell count of the cerebrospinal fluid. Furthermore, the roentgen-ray picture of specific spondylitis has none of the ear-marks of tuberculous caries. There is never any real crushing of the bone, and the changes are always much more on the periphery than in the center of the vertebræ. It is much more difficult to differentiate the roentgen-ray picture of these specific forms of spondylitis from that of other forms of chronic spondylitis, especially spondylitis deformans. Dr. Jaches, whose opinion on this subject I value most highly, hesitates to decide from the roentgen-ray findings alone whether or not a given case be luetic. If, however, the examination of the blood and spinal fluid, the roentgen-ray findings and the rapid improvement following upon specific treatment suggest the specific character of the disease, it would be straining a point not to recognize specific spondylitis as the most plausible diagnosis.

The occurrence of such forms of spondylitis in association with tabes, as I have seen in a few instances, tends to strengthen the belief in the relative frequency of this form of spondylitis.

Without wishing to burden this paper with detailed histories

I shall refer to a few cases that are entirely typical of the various forms to which I have alluded.

The patient, L. C., presented at the meeting is still under observation at the hospital.[2] He was admitted only a few weeks ago markedly paretic in the upper extremities with very limited motion of the head and with a general spinal rigidity; he also gave a history that a number of months ago, at another hospital, he was operated upon in the mid-dorsal region because of the symptoms which he presented and the radiating pains and possibly definite areas of disturbed sensation. Nothing abnormal was found. I have no fault to find with this operation, for I remember some twenty-odd years ago having caused a similar operation to be done upon a patient who presented such symptoms, and who at the time of the operation revealed nothing but a very much thickened dura and a formation of tense fibrous strands on the inner surface of the laminæ. In this same instance there was a distinct improvement in the carriage and in the general condition of the patient after the operation. In this present case no improvement was noted after the operation: the patient became worse, the affection in the cervical regions evidently becoming much more severe until he was compelled to come to the hospital for relief.

His condition on admission may be summarized briefly as follows: Rigidity of the neck; marked limitation of movement of the upper extremities; pain along the course of both brachial plexuses; exaggerated biceps and wrist-jerks; gait somewhat spastic; lively deep reflexes in lower extremities; Achilles reflexes very lively; abdominal reflexes also lively; entire vertebral column rigid, with tenderness over cervical, lumbar, and sacral spines; scar of operation over lower half of thoracic region; hyperesthesia and hyperalgesia and increased sensitiveness to cold over both lower extremities anteriorly and posteriorly from the level of the crest of the ilia. The Wassermann reaction of the blood was $++++$. The roentgen-ray findings were: "Marked degree of spondylitis in the 4th, 5th, and 6th cervical vertebræ; in the 11th and 12th thoracic and in the 1st lumbar vertebræ; an apparent diminution in size of the 5th lumbar vertebræ."

Once the specific character of the blood was determined active treatment was instituted, the patient receiving intravenous and intramuscular injections, and the result has been most gratifying, the patient at the present time being able to raise his arms and to use his hands, and has also begun to move his head quite freely.

Another patient whose disease was of special interest was A. P., aged thirty-four years, a clerk, who was admitted to Mt. Sinai Hospital on October 29, 1912. He was then married four and a half years; had no children; his wife has had no miscarriages. His

[2] In February, 1916.

family history was practically negative. According to his own statement he had acquired gonorrhea and syphilis about ten years previously. He received at that time ten mercurial injections and was given mercury by mouth. So far as he knows there were no secondaries. About eight months before admission to the hospital he had painful stiffness of the neck lasting three weeks. Four months ago the pain returned and was located in the upper part of the back and neck radiating to the collar-bone and middle of both arms. The pain was persistent, worse at night, and was aggravated by any sudden jar or rotation of the head. He also stated that during the past few weeks he had some difficulty in swallowing food, as he thought, because of some swelling in the throat. He had no fever or cough, but occasionally had some night sweats. There was no dyspnea, no bladder disturbances, and no sensory disturbances.

The patient presented a marked limitation of motion of the head in every direction. The head was practically fixed. Behind the middle of the left sternomastoid muscle, and also on the right side in the same position, there was a small, hard, nodular mass. There was marked tenderness to pressure over the upper four cervical spines, a marked prominence of the second cervical, and a slight right scoliosis in the cervical region. His gait was normal except for his modified carriage. The reflexes were normal and there were no other objective symptoms.

The swelling on both sides of the neck, the pain on pressure on both sides of the spines, pointed strongly to an involvement of the vertebræ. Shortly after admission the Wassermann reaction of the blood was positive; the cerebrospinal fluid was negative. The roentgen picture as developed by Dr. Jaches showed that the body of the fourth cervical vertebra was greatly destroyed, more markedly on the left than on the right side. The lower part of the third and the upper part of the fifth vertebræ were slightly eroded.

The patient was put on salvarsan treatment. On November 4 he was given 0.4 intraveneously; on November 15, 0.3, and on November 27, 0.4. After the first injection the pain was distinctly lessened; after the second we noticed a marked improvement, and after the last treatment the condition showed very satisfactory improvement. He was discharged from the hospital on December 4, able to move his head in every direction and entirely free of pain. He returned to the hospital for observation a number of times. A second series of roentgen-ray plates proved that the bone process was undergoing resorption.[3] If all signs do not fail us it is fair to claim that in this the wry-neck was due to syphilitic caries of the cervical vertebræ.

Resembling this very case is that of another patient, aged fifty-

[3] The roentgen-ray evidence of improvement in this case was most convincing.

six years, J. R. H., who gave a distinct luetic history, and whose symptoms were not unlike those previously recorded. He complained of pain in the left shoulder radiating down the left arm; of weakness in the left upper extremity, and of pain in the back, for two months previous to admission to the hospital; also of paresthesia in the right lower extremity.

On examination we found tenderness in the left shoulder; wasting of the muscles of the left shoulder girdle and of the left forearm; distinct wasting of the thenar and hypothenar eminences, and wasting of the interrossii. The grip of the left hand was weak. There was also hyperesthesia of the right half of the scalp and of the right upper extremity except in the hand. The Wassermann reaction of the blood and of the spinal fluid was negative, but there was distinctly increased lymphocytosis of the cerebrospinal fluid and 97 per cent. lymphocytes.

In this case again the roentgen-ray examination revealed a spondylitis of the 5th, 6th, and 7th cervical vertebræ and a very slight lesion in the third and fourth cervical. In such a case as this there may be some doubt as to whether we can positively claim that the spondylitis is of specific origin, although there is considerable temptation to put such a case as this in this category, and, indeed, it leads us to suspect that a number of the cases of generalized spondylitis of unknown origin may, on closer examination, prove to be specific.

After setting aside the specific cases of spondylitis a number of others remain, occurring in middle age both in men and in women, possibly a little more frequently in the former, exhibiting rigidity of the spine, radiating pains, slight kyphosis, and varying in intensity of deformity from very slight to such forms as bear the closest possible resemblance to the typical cases of spondylose rhizomélique. The recognition of these cases is dependent very largely upon the roentgen-ray findings, and here the irregularity in contour of the vertebræ, the evidences of osteophytic growths, the slight lipping of the vertebræ, lead to the correct diagnosis. There is no doubt that in these forms as well as in the specific there is considerable exudate, considerable thickening of the periosteum and of the meninges, all of which is not revealed on the roentgen-ray plate. And, on the other hand, it is also fair to assume that this same diagnosis may be found in persons who present no tangible bone or nerve symptoms I suspect that in many cases the symptoms are due to the exudate and to the thickened meninges rather than to the altered condition of the vertebræ themselves that are shown more or less distinctly on the roentgen-ray plate. The same roentgen-ray findings also occur in the senile period, at least as frequently in women as in men, and are often associated with other arthritic changes that are common in this period of life. We have found these senile forms of spondylitis in a number of elderly persons

who have either presented symptoms of sciatica, changes in the sacro-iliac juncture, or symptoms pointing to a lumbar arthritis. The occurrence of spondylitis deformans in association with a general arthritis deformans goes without saying.

Considering the etiological factor in all of these forms of spondylitis, barring the specific, it is reasonable to suppose, as some of the French and German writers have maintained, that many of them are expressions of some chronic infection[4]. Some such have been reported as occurring after streptococcic pleuritis and after scarlet fever, diphtheria, measles, and whooping cough. That some of them may be of gonorrheic origin must also be admitted.

I am willing to join those who believe that very few of these cases will prove to be allied to the purely rheumatic disorders and yet cases do occur in which an ordinary spondylitis appears in association with general articular rheumatism. For that reason, if for no other, it will not do to discard wholly the group of rheumatoid spondylitis.

The difficulty that arises in the differential diagnosis is concerned chiefly with the question of deciding whether or not, in a given case, we are confronted with spondylitis or with spinal neoplasm. In primary neoplasm of the cord there would be very little difficulty. The roentgen plates often do not offer the expected help. In many instances we have observed spondylitic processes in the vicinity of spinal neoplasm. The entire and more rapid march of the symptoms will, as a rule, point the way to the correct diagnosis. But particularly in the cases of secondary carcinomatous and sarcomatous deposits a mistaken diagnosis can be made readily enough, although even in these forms the more rapid progress of the symptoms and the early involvement of the spinal cord and relatively slight involvement of the vertebræ will turn the scales in favor of neoplasm rather than of spondylitis.

So far as the treatment of these cases is concerned the specific cases should be treated most vigorously by intravenous injections of salvarsan, combined with intramuscular injections of mercury or by inunctions. The non-specific cases must be treated either by simple rest, by intense heat, or by such measures as it is entirely within the province of the orthopedic surgeon to suggest.

[4] Dr. Nathan's views on the infectious origin of chronic spondylitis as reported at this same meeting are of great value.

THE NEUROLOGICAL CONDITION ASSOCIATED WITH POLYARTHRITIS AND SPONDYLITIS.[1]

By Philip William Nathan, M.D.,
NEW YORK CITY.

(A Clinical and Experimental Study from the Montefiore Home and Hospital, and the Carnegie Laboratory, Pathological Department.)

That symptoms referable to the nervous system are not infrequently associated with both acute and chronic joint disease has been recognized by all those who have studied these conditions. Even the earliest writers comment upon this association and speculate upon the interrelation of these conditions. However, even with the improved methods of clinical investigations and the more intensive studies of modern times, the nerve conditions associated with acute and chronic arthritis have not been definitely determined, and the relation between nerve and articular conditions still remains unexplained.

This is true not only of the acute and chronic polyarticular conditions which do not seriously involve the spine, but in spite of the impetus given to the study of the arthritides of the spine, by the researches of Bechterew, Strümpel, and P. Marie, it also remains true of the neural phenomena of vertebral arthritis.

Nearly all the writers upon these conditions content themselves with the mere statement that certain symptoms referable to the nervous system occur in cases of mono- and polyarthritis; and those who comment upon the causal relationship between these conditions at all seem content to follow Charcot in his view that the neural symptoms are due to the reflex influence of the arthropathy.

This, in spite of the fact that there are numerous cases on record which show definitely that the neural symptoms cannot, for obvious reasons, be due either directly or indirectly to the arthritis itself. So, for instance, there are not a few reports of amyotrophic lesions associated with, but in no way corresponding to, the distribution of arthritis following gonorrhea; and there is not an insignificant literature upon the same neural lesions which have followed infections in which the joint lesions have been evanescent or absent entirely.

My own experience has led me to believe that, aside from the atrophy and hypertonia which can, with more or less propriety, be attributed to reflex action, neurological symptoms are frequent accompaniments of polyarthritic conditions; that these symptoms are definite, and that they bear a definite relation to the underlying morbid process.

[1] Read before the New York Neurological Society, December 7, 1915.

These neurological phenomena, which for the most part consist of muscular atrophy with spasticity, vasomotor irritation, and disturbed sensation, may be associated with either acute or chronic polyarthritis.

During the acute stages when the joint symptoms and the general reaction is marked the neural symptoms are rarely looked for, and for this reason not often described. Since I have made a practice of making a neurological examination of all patients with polyarthritis, I have found transient, and more or less permanent, spastic atrophic phenomena, evidently not of reflex origin, in a considerable number of cases of acute polyarthritis. The symptoms are not present in all, and in a considerable number of cases they are mild and continue only for a short time; in a certain percentage of the cases, however, they are pronounced and definite. The following abstract of the history of a case of acute goneitis seen in a ward of one of our best city hospitals illustrates both the tendency to overlook these symptoms entirely and the usual symptom-complex during the early stages.

A. B. became suddenly ill with intense pain running down the left lower extremity from the pelvis to the foot; the following day the left knee became swollen and extremely sensitive; he had high temperature and marked general indisposition. He was brought to the hospital, where he was given the usual antirheumatic treatment. The pain and the swelling of the knee gradually subsided, but did not wholly disappear. When I saw him, three weeks after admittance, he complained of pain in the knee and weakness in attempting to walk. The patella and Achilles reflexes were markedly exaggerated, and he had an inexhaustible ankle-clonus on both sides. The condition gradually improved.

I have found similar spastic paretic conditions, involving either the upper or lower extremities, associated with joint infections as sequelæ of gonorrhea, pneumonia, sepsis, and typhoid fever. In some instances the neuromuscular phenomena were the only neurological symptoms; more often there were also symptoms referable to irritation of the sensory nerves (hyperesthesia, radicular and lancinating pains), and occasionally vasomotor and so-called trophic skin disturbances (localized hyperidrosis, glossy skin, and edema) were also present.

The phenomena of vasomotor irritation are not likely to occur during the early stages of the chronic, and, with the exception of the hyperidrosis, are rare in the acute self-limiting conditions.

In a very considerable number of the acute infections the phenomena of neural irritation ultimately subside irrespective of the outcome of the joint disease. In some cases, however, the neurological condition persists much longer than the joint abnormality, and, in certain cases, muscular atrophy and spasticity remain as the only permanent change.

A fairly large number of the cases of chronic deforming arthritis are accompanied by musuclar atrophy and a varying degree of spasticity. The location, the duration, and the intensity of these neurological symptoms are extremely variable; and though in some instances their intensity and distribution correspond to the joint involvement, in a large proportion of the cases the two morbid phenomena are independent of each other. Thus, in some cases the joints of the upper extremity only are involved, but the atrophy and spasticity are present in the lower extremities as well; and not infrequently the abdominal and facial muscles are also involved.

In many of the cases muscular atrophy and spasticity is the earliest symptom. It not only precedes the joint involvement by a considerable interval, but it may remain the most prominent symptom throughout the course of the disease. And I not infrequently see patients with marked disability, supposedly due to polyarthritis, in whom the joint disease is insignificant, the disability being entirely due to muscular atrophy, spasticity, and permanent muscular shortening. This is unusually well illustrated in the following case:

M. M., male, aged twenty-eight years. Admitted to Montefiore Home, March 6, 1914. The disease began with pain in the right thenar eminence three years ago. Pain gradually extended first up the right arm, and within three or four days all four extremities were involved. The hands, knees, and feet were swollen. Pain and swelling subsided after a few weeks. He then noticed that his extremities were stiff and weak and he was unable to walk. He complains that he has grown weaker and more stiff during the past three years, though he has no pain when he is quiet or when the passive motion in the joints is not forced.

Chief Complaints. Stiffness and weakness of extremities. Inability to walk.

Physical Examination. Heart, lungs, and abdominal organs show no abnormalities. Blood-pressure, 122; Wassermann, negative. Contraction palmar facia of right hand; marked atrophy of thenar hypothenar eminences and the interossei of both hands. Both elbows are flexed to right angle by muscular shortening or contracture; the motion is not limited by actual joint changes, and is not painful unless forced beyond the limits maintained by muscle shortening. In the shoulders there is limitation of abduction only, the other motions, particularly rotation, being free. Both hips are flexed to almost a right angle, extension being limited by shortening of the flexor muscles. Abduction is also limited by adductor contraction; all other motions are free, and there are no evidences of active disease in the hips. Both knees flexed, the hamstrings are contracted, and motion is further limited by change in the joint structures. The feet show no signs of joint disease. Motion in the spine is partially limited. There is marked muscular atrophy and

marked exaggeration of the reflexes in all four extremities and ankle-clonus on the left side. He is unable to walk because of the weakness and spasticity. The very insignificant changes in the knee are the only evidence of permanent arthritic condition.

Such a marked degree of spastic paresis without other lesions is, of course, unusual. But spastic paretic phenomena are not uncommon accompaniments of all forms of chronic deforming arthritis. It is true they are not present in all cases, and when present they are usually mild in character; they may, however, be, as in the case just cited, so marked that they completely overshadow the joint condition. Occasionally, indeed, as in the following case, the segmental nature of the lesion is even more strongly suggested by the clinical phenomena:

B. C., male, aged forty years. Admitted to Montefiore Home December 19, 1913. One year ago he began to have pains in the fingers of the right hand, but continued to work. Soon afterward he noticed a swelling of the joints between the proximal and middle phalanges of the index, middle, and ring fingers. The pain and swelling increased in severity and soon extended to his right elbow joint and then to his right shoulder. The above joints also became somewhat swollen. Following this his neck became somewhat rigid, and he began to have severe pains in his left chest. He was sent to Gouvenor Hospital, where he remained for six months. Under treatment there was considerable improvement, and he was able to go back to work again.

He worked for about two weeks, when his knees became very painful and swollen, so that he could not walk. Soon after his hips, ankles, and the fingers of the right hand became involved.

Status taken by Dr. Elliot: No cardiac, renal, or pulmonary symptoms.

Right hand: Linear globular swelling of the proximal midphalangeal joints. Carpophalangeal and phalangeal joints of the thumb enlarged and sensitive to pressure. Distal phalangeal joint is enlarged. Motion is restricted.

Right elbow can be flexed to an angle of 45 degrees and can be extended to 135 degrees. Supination and pronation restricted.

Motion in right shoulder somewhat restricted, but all movements are present.

The conditions in the left hand and fingers are the same as in the right. There is more fulness of the metacarpophalangeal joints of the index finger. Flexion and extension is apparently normal. Supination and pronation restricted on account of pack in carporadial joint. Motion in the left elbow and shoulder practically normal.

Motion in both ankles is painful. Passive motion is normal. Both knees are painful to pressure; contour is obliterated by swelling and doughy in character. The patellæ are mobile.

There is thickening of the periosteum of both ilia, and they are very sensitive to pressure.

Urine: Negative for albumin, sugar, indican. Microscopic examination negative.

Blood-pressure, 120.

Wassermann: Negative.

Blood: Hemoglobin, 85. Red blood cells, 4,400,000. White blood cells, 10,200; neutrophiles, 60; eosinophiles, 2; small lymphocytes, 20; large lymphocytes, 14; large mononuclear leukocytes, 2; basolymphocytes, 1; myelocytes, 1.

Status when he came on my service (January, 1915) was as follows:

General condition poor. He walks with marked spastic gait and can only get around with considerable difficulty. He has no pain when quiet, but has considerable pain on flexion and extension of the knee. He can voluntarily extend the knee after some effort, when it becomes stiff in the extended position. After much effort he can gradually flex the knee after it has been extended, when the knee becomes stiff in the flexed position; that is, he has alternate flexor and extensor spasm of the muscles of the knee.

A similar condition exists in the right hand. As a rule, he has spasm of the extensions of the fingers. When, however, the flexors are irritated (struck with a percussion hammer a few times) the spasm leaves the extensors and affects the flexor muscles. The left hand is free. The right abdominal reflex is much more marked than the left. There is marked muscular atrophy of the muscles of the right hand, arm, and both lower extremities.

The spine is somewhat stiff, but not completely immobilized. There is pain on percussing the spines in the upper dorsal and dorsolumbar regions. There are no signs of active joint disease anywhere.

Such motor phenomena as I have here illustrated may or may not be accompanied by sensory and vasomotor disturbances. Radicular and lancinating pains are very often present in acute polyarthritis and during the early stages of chronic deforming arthritis. Paresthesia, particularly akroparesthesia, are very common; and transient and long-continued hyperesthesias are present in a very large proportion of the cases. Definite segmental areas of anesthesia are here, as in analogous conditions, difficult to demonstrate.

Vasomotor symptoms and the so-called trophic skin lesions are not as common as the other neurological symptoms. When they are present there is always some neuromuscular abnormality, though such symptoms may exist without signs of sensory involvement. The gravest cases of so-called rheumatoid arthritis are those in which severe generalized joint involvement is associated with spastic paretic and vasomotor changes. In these cases the muscular atrophy is often extreme, the skin is thin and markedly edematous

or glossy, and the blood-pressure remarkably reduced. Decubitus ulcerations of the skin, degeneration of the nails, etc., make the condition of the patients pitiable. Fig. 1 shows the extreme atrophy

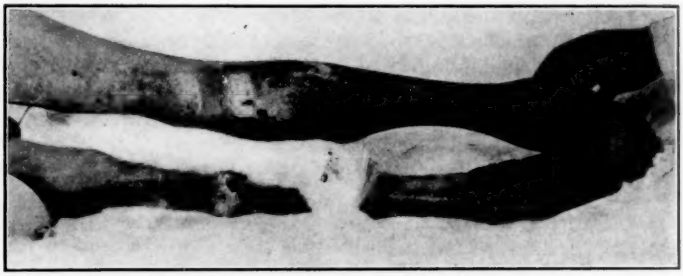


FIG. 1.—Extreme muscular atrophy, pigmentation and ulceration of the skin in deforming arthritis with radicular involvement.

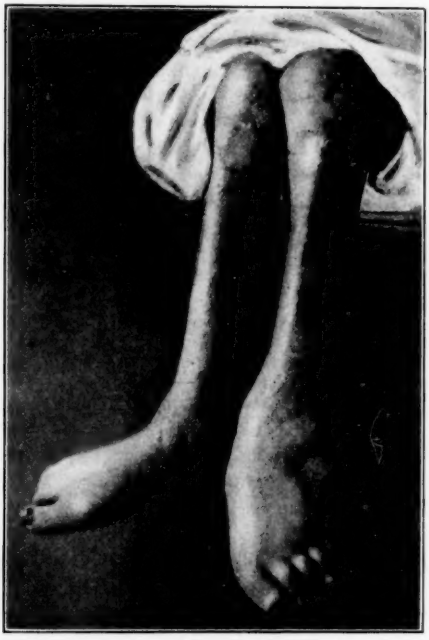


FIG. 2.—Neurotrophic edema, ulceration, and pigmentation of the skin in a case of deforming polyarthritis with radicular involvement.

and trophic skin disturbance in such a case. Fig. 2 shows another case of chronic deforming arthritis with amyotrophy and (so-called) neurotic edema.

Various combinations and all degrees of these evidently organic neurological phenomena are to be found in the various forms of polyarthritis. They occur in cases with and without evident vertebral involvement; they may be severe in cases of mild joint disease; they may be mild or absent in long-continued and severe forms of generalized arthritis; they may be transient or permanent; and they may or may not be combined with signs of organic disease (heart, kidneys, etc.) elsewhere. Moreover, though the condition may soon become stationary or completely disappear, after the signs of general illness have subsided and the joint symptoms are no longer progressive there are cases in which the neurological condition progresses just as it does in amyotrophic spinal conditions, invading segments from above downward, or *vice versa*, with or without definite regularity.

To judge from the variability of the neurological symptoms the deleterious influence which attacks the spinal nervous system in these cases must vary considerably in intensity, the region or regions it attacks, and the manner in which it produces the pathological changes. However, notwithstanding the extreme variability in location and intensity, the fundamental constituents of the neurological symptom-complex are practically always the same, namely, a hypertonic paretic condition with or without disturbed sensation, and vasomotor and trophic skin abnormalities.

Only in rare instances does one find definite areas of anesthesia associated with a hypertonic condition, and equally infrequent are flaccid paralyses of individual muscles, with or without hypertonic conditions elsewhere.[2]

If now we turn to the symptoms which are present in the evidently vertebral arthritides we find the same variability as to the intensity and to the location of these conditions, and the same absence of a definite relation between the intensity and in many cases even in the location of the neural and articular lesions. Since Bechterew, Strümpel, and P. Marie have published their findings the literature on this subject has grown steadily more unwieldy; many classifications of the vertebral condition both as it relates to character of vertebral involvement, to the joint involvement elsewhere, and as it relates to the neurological status, have been proposed, but so far no one has been able to show that there is a definite relation between these conditions.

The symptoms described by Bechterew are fundamentally the same as those we have just shown to be associated with arthritic conditions generally, namely, spastic atrophic, hypertonic, and irritative sensory phenomena, with occasional anesthesia and flaccid paresis.

[2] In a case recently admitted to the Montefiore Home there was a paretic condition of the left gastrocnemius muscles, absent Achilles reflex, associated with polyarthritic and spastic paretic changes elsewhere.

From my own material, which is considerable, and from the case reports I have been able to find in the literature, the neurological condition apparently bears absolutely no definite relation to the character of the joint lesions. Definite nerve symptoms may be present in cases with marked spinal stiffness, with kyphosis, lordosis, or lateral deviations of the spine; they may be totally absent in cases presenting exactly similar ankylotic and deforming conditions. Cases with practically very little deformity without any

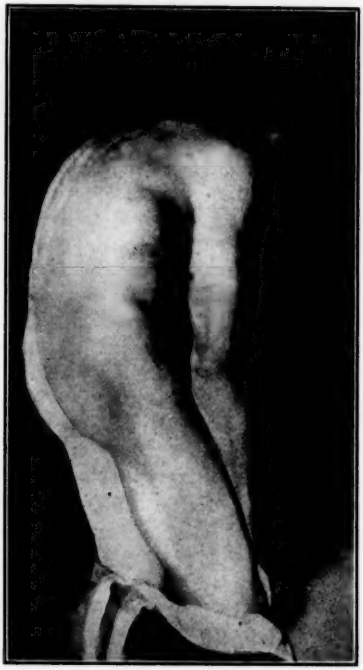


FIG. 3.—Infectious arthritis of the spine with complete ankylosis. There is no radicular involvement and, except for the deformity and stiffness of the spine, this man is perfectly well.

ankylosing condition may, on the other hand, present marked motor and sensory abnormalities, while others with complete bony ankylosis of the bodies of the vertebræ and even the costovertebral joints may show no neurological change whatsoever. Fig. 3 is a picture of a negro with complete vertebral ankylosis and marked kyphosis without neural involvement. This boy continues his occupation as newsboy without apparent discomfort.

Nor does the fact that the hips or the shoulders are involved

seem to bear any relation to the presence or absence of the neurological symptoms. These symptoms are just as often conspicuous in the types of Strümpel and Marie as they are in the one described by Bechterew,[3] and equally as often totally absent in the final stages of the conditions.

As far as the spondylitis is concerned this variability of the symptoms may be partly explained on the ground that the neural phenomena may be present during the early stages of the disease and disappear at some later time; or, on the contrary, the neurological changes may come on insidiously, when they will, of course, be absent during the early stages. Thus it will depend upon the period when the patient comes under observation whether these symptoms are definitely present or absent. But this only partly explains the condition of affairs, for it does not account for the variability of the symptoms themselves nor for the fact that in some cases the symptoms are absent throughout the course of the morbid process.

I have for sometime thought that all the peculiarities here enumerated could be readily explained upon purely anatomical and mechanical grounds, but the difficulty in procuring autopsies in such cases has made the actual demonstration of the lesions in the human subject impossible.

It must be evident to everyone who has had neurological experience that the neural symptoms here described must be due to nerve-root irritation or compression, and in the very severe cases, perhaps actual spinal-cord compression. Curiously enough, few of the writers upon this subject have thus interpreted these symptoms; nor, except in a few instances, are the conditions in the epidural space, the intravertebral foramina, and the costovertebral joints considered in the autopsy reports to be found in the literature. It is not surprising, therefore, that actual neurological findings have been for the most part negative, and the actual causal relation between the joint and neurological conditions has remained unexplained.

When, therefore, I found that I could induce chronic non-suppurative polyarthritis in animals, I immediately determined to examine the conditions in the vertebræ and the spinal canal in order, if possible, to demonstrate morbid changes in these structures. The results of these investigations are here presented.

It has been shown by J. Koch that the bone marrow, like the liver and spleen, is influential in filtering microörganisms from the blood. Microörganisms can nearly always be recovered from the bone marrow in the spongy portions of the bones, when they have been injected into the blood stream of animals, and they are practically

[3] Unless one chooses to classify only those cases of spondylitis with neural symptoms as belonging to the Bechterew type.

always found in these situations in the human subject dead of an infectious disease.

J. Koch was enabled to produce polyarticular conditions in the dog (much resembling acute arthritis in man) by injecting streptococci. In a number of his animals he secured polyarticular conditions which markedly resembled the acute polyarthritis usually designated as acute articular rheumatism.

The results of my own experiments confirm the findings of Koch in every particular. I have found that following the injections of hemolytic streptococci I could produce various forms of bone and joint lesions. These lesions were in some cases acute, in others they were subacute or chronic. Actual suppuration never supervened. Of eighteen dogs which received the streptococci directly into the femoral vein, six showed both clinical and postmortem bone and joint abnormalities in the spinal column.

After a stage of incubation which lasted about three days, all the animals had a rise in temperature and signs of general indisposition. Following the initial rise in temperature, the six animals which showed the vertebral changes postmortem seemed to be disinclined to walk and also seemed weak on the legs. The joints, however, though swollen, were not apparently painful, and the disability was evidently due to weakness. In one of the dogs (dog 2 of my series 1) the joints were apparently unaffected. But this particular animal, like the others which had spinal involvement, remained weak even after the temperature had subsided (a few days after the onset of the symptoms), and died twenty-eight days after the injection of the bacteria.

With the exception of the last mentioned the animals with spinal involvement were killed on the eighth, sixteenth, twenty-first, forty-eighth, and ninetieth day after injection, respectively.[4]

The conditions of the bones and joints generally will be fully described in another paper. What is of interest here as bearing upon the spinal condition is the fact that during the earlier stages of the disease, besides the changes in the epiphyseal marrow, the infection involves the subperiosteal region of the epiphysis. The inflammatory condition spreads from this situation to the region of the capsular insertion and thence directly invades the capsule itself and the joint interior.

Joint swelling, when present, is due not alone to increase of the joint fluid, but during the earlier stages it is due to peri- and para-articular exudate as well. This peri- and para-articular exudate was present in all the animals which showed joint involvement at all, when the animals were killed during the early stages of the disease. The exudate was not bacteriologically examined in my

[4] The protocols are omitted to save space. They tally, with the exceptions mentioned, with those of Koch.

cases, but Koch found it sterile in all his cases, even when the streptococci could be demonstrated in the epiphysis.

As has been said, in six of my cases there were changes in the spine. On opening the spinal canal one immediately became aware of an epidural exudate. The epidural areolar tissue was markedly edematous, of a gelatinous consistency, and in some places completely filling the epidural space with a semisolid opaque mass. The location and extent of the edema was irregular. In one case it extended continuously from the middorsal to the lumbar region.

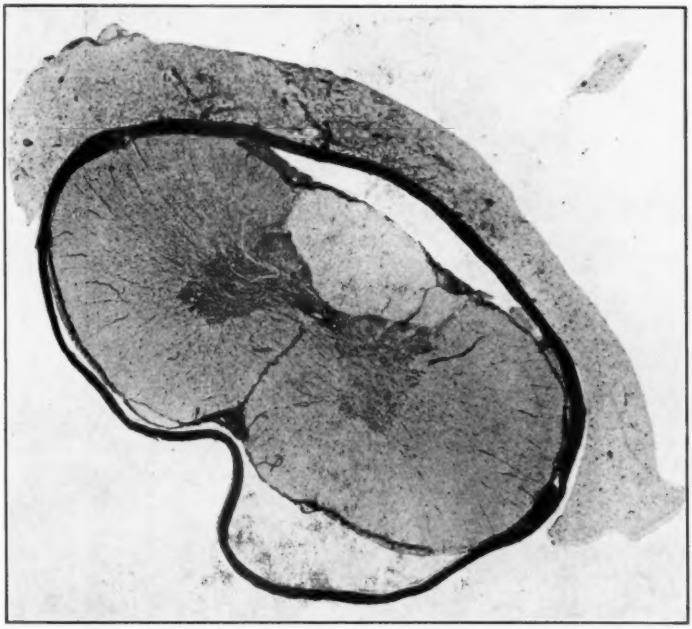


FIG. 4.—Section of spinal cord showing beginning of organization of the exudate on the dura.

In the others the exudate was discontinuous and involved one or more areas, varying in extent and location. Except where the edematous and thickened areolar tissue was closely adherent to the dura the dura and the spinal cord showed no changes microscopically. The vertebral veins were markedly dilated and congested (Figs. 3 and 4).

A number of the costovertebral joints were involved in all the cases. These presented both an intra- and peri- and para-articular exudate in the earlier stages. Later there was considerable thick-

ening of the connective tissue in their neighborhood, and there was distinct beading at the epiphyseal junction of the rib.

The periosteum of the vertebral bodies was distinctly thickened in a number of situations. Both the lower and the upper (*i. e.*, the celomic and the side facing the spinal canal) were so changed, but the location and extent of the thickening was extremely irregular. In some cases (dog 3 which died on the twenty-eighth day) the

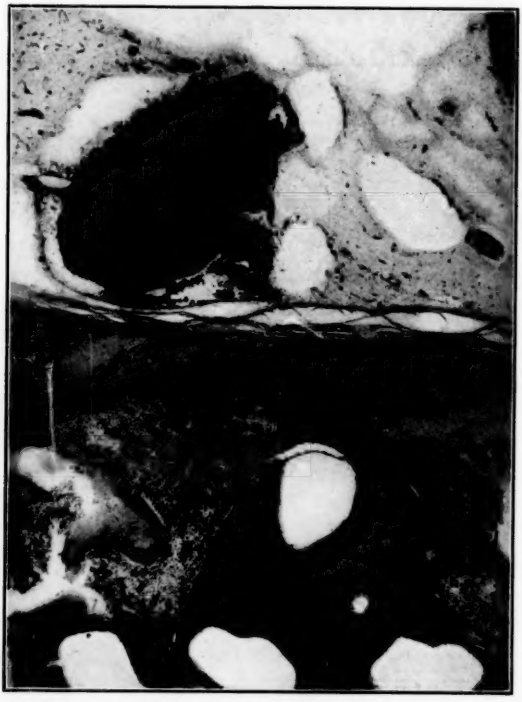


FIG. 5.—Epidural surface of body of the vertebra. Exudate under the periosteum and in the epidural space. Dilated vein containing thrombus. The hyperemia and medullary cell proliferation is also shown.

bodies of nearly all the thoracic vertebræ were involved, and the surface of the vertebræ on both sides present a somewhat nodular appearance macroscopically. In dog 1, killed on the eighth day, the thickening of the periosteum could not be seen macroscopically. In dog 6 only three vertebræ seemed to be affected.

The affected vertebræ were distinctly softer than the normal in all the cases and could be sawed through with considerably less difficulty than those of the normal dog. There were no signs of

actual deformation in any of the cases, and in only one dog (No. 6) was there any evidence of involvement of the vertebral synchondroses with rather insignificant limitation in the movements of the spine.

Microscopically the structure of the vertebral bodies showed changes corresponding to those found in the epiphyseal ends of the long bones. There was marked increase in the blood supply and gradually increasing hyperplasia of the marrow cells. The marrow

FIG. 6.—Exudate surrounding spinal ganglion. (*a*) Vein containing thrombus. (*b-c*) Extravasated blood.

cells increased in numbers until they completely filled the marrow spaces, and continuing to proliferate the cells encroached upon and gradually displaced the bone trabeculæ. Then more and more bone becomes absorbed, neighboring marrow spaces become confluent, and the bodies of the vertebræ become rarefied. In some situations the rarefication is extreme (for instance in dog 5, forty-eight days), the bone trabeculæ are very few in number, very thin, and the body of the vertebræ almost completely made up of lymphoid marrow.

The details and the termination of the marrow changes cannot be described at the present time. They are, as has been said, similar to those found in the epiphysis of the long bones, and will be more fully considered in another paper. One fact, however, must be emphasized, namely, the changes in the bone may subside and the bone trabeculæ are then more or less completely restored.

What interests us particularly at the present time are the subperiosteal and juxtaperiosteal changes. These changes affect both the celomic and the epidural sides of the bodies of the vertebræ, and in both the conditions are similar. More important, because of their bearing upon the neural involvement, are the morbid conditions as they affect the epidural periosteum. Here, as elsewhere, the disease is at first focal. The focus may spread rapidly, or a number of foci become confluent, and there is a considerable hyperemic area. Following the hyperemic stage the subperiosteum becomes edematous and as the pathological process advances the adjacent structures become edematous as well. In some cases the edema subsides, leaving the adjacent tissue spaces dilated, or the edematous condition is followed by connective-tissue proliferation, when the nodular condition of the periosteum, referred to above, ensues.

I have not been able to demonstrate the streptococci in the lesions here described, but these lesions correspond exactly in their essential features with those which occur elsewhere, and in which J. Koch has demonstrated the presence of the injected organisms.

Coincident with the subperiosteal changes the tissues in the neighborhood become congested and edematous. The periosteum is raised from the underlying bone and the edema spreads to the neighboring areolar tissue in the epidural space, intravertebral notches, etc. It is to be noted that these changes, particularly the exudate, correspond exactly to the peri- and para-articular exudate of the joints of the extremities, and for this reason the exudate is in all probability sterile. This is an important consideration, for it accounts for the fact that the actual inflammation, as far as the findings in the present series are concerned, did not extend to the dura.

In some, but not in all the cases, the epidural exudate became organized. My work in this respect is not complete, but so far as I can make out at the present time it appears that the epidural exudate may be completely absorbed, or it may become generally or locally and to all appearances permanently organized. At any rate I have found definite signs of organization and localized areas of connective-tissue proliferation in several of my cases.

The condition in or near the costovertebral joints, and in the neighborhood of the intervertebral notches, differs in no way from those just described. In the epiphyseal ends of the ribs the tendency to connective-tissue proliferation and permanent periosteal

thickening is much more conspicuous and leads to the condition referred to as beading of the ribs, and to coarctation of the intervertebral foramina.

It is impossible, without greatly exceeding the time at my disposal, to describe the microscopic findings in detail. It is evident that the morbid conditions in the spine and the adjacent tissue in streptococcus infection in the dog are fundamentally the same as those found in other parts of the skeleton. There are both endosteal and subperiosteal processes which are manifest, clinically and pathologically, by intra-, peri-, and para-articular joint exudations in the early stages, and which are followed by transient relaxation or more or less permanent connective-tissue hyperplasia. In the diarthrodial joints I have been able to follow the process still further. For the present purpose, however, the demonstration of the changes to the point of connective-tissue hyperplasia is sufficient.

The mere fact that there may result an epidural exudate as a result of streptococcus infection is illuminating. That similar conditions may be and are very likely present in the human subject is borne out not only by the fact that we can demonstrate symptoms which strongly suggest that such a condition may exist, in many cases of polyarthritis in man, but the analogy is still more strongly suggested by the fact that the marrow changes and microörganisms have been demonstrated in the human subjects. Fraenkel was able to demonstrate the presence of the typhoid bacillus and the pneumococcus in the marrow of the bodies of the vertebræ in a number of cases dead of these diseases. And although he does not describe the periosteal and the epidural conditions which I have found present in the dog, his description of the marrow changes are certainly analogous. Moreover, Bechterew in his report of the autopsy of one of his cases describes changes in the epidural space involving the nerve roots, which are certainly analogous to those I have here described.

That the streptococcus, pneumococcus, gonococcus, and no doubt other microörganisms may cause analogous conditions in the joints and peri- and para-articular structures is well known. The clinical manifestations of such a morbid condition are common in cases of general infections due to a variety of microörganisms, conspicuously so with the gonococcus infection.

As analogous conditions exist in the other joints and similar marrow changes and microörganisms have been demonstrated in the bodies of the vertebræ in the human subject, it seems to me only fair to assume that similar or analogous epidural conditions must be held accountable for the neural symptoms in the human subject.

That such conditions completely account for the neural symptoms is evident. The symptoms present in all forms of arthritis, whether acute or chronic, early or late, are those of radicular or spinal irritation or compression. These symptoms, transient or permanent,

mild or severe, complete or incomplete, can only be caused by changes not in the roots themselves but to altered mechanical conditions in the epidural space or the intervertebral notches.

When there is extensive inflammation and exudation the symptoms will be severe and extensive in distribution; when the condition comes on acutely and subsides we may have, as we often do, severe but transient neurotrophic conditions. In some cases the clinical manifestations are those of a localized process, in others the symptoms are those of a chronic, transient, or a permanent change in the juxtaradicular region.

In the dog the pathological changes correspond exactly to such clinical phenomena. There are cases in which the exudate and the inflammatory changes are more or less localized, those in which it pursues its course insidiously (dog 6, which never showed marked indisposition, but gradually became slightly lame, and when killed on the ninetieth day was found to have only two localized nodes of connective tissue near the intervertebral notches of the fifth and seventh thoracic vertebræ) and those in which the morbid process had apparently led to permanent changes.

It is evident, too, that the infectious process in the dog may lead to definite interference with the functions of the spinal roots without actually interferring with the gross mobility of the spine, which again readily suggests why in some cases we have pronounced symptoms of root involvement in the human subject, though the spine is only partly or not at all immobile.

On the other hand, the fact that the spine may be more or less completely immobile and even markedly deformed, without recognizable symptoms of neural involvement, does not, at first sight, appear so easily explained. When, however, it is considered that the disease may involve the thoracic or abdominal side of the bodies of the vertebræ and the intervertebral syndroses, or the small joints of the spine, and there cause the permanent changes which lead to ankylosis; and that in this case the epidural changes, if they have existed, were transient, the reason why neural symptoms may be absent in such cases becomes apparent. On the other hand, it goes without saying that epidural conditions, and as a consequence clinical manifestations of radicular or even spinal compression, may be, as they are in tuberculous spondylitis, coexistent in such cases.

If then my assumption that the pathological conditions are analogous to those we find in the experimental conditions in the dog is correct, neural symptoms associated with polyarthritis and spondylitis are caused not by the actual involvement of the nervous system in the pathological process, whatever its nature, but by mechanical conditions which supervene either during the activity of or after the actual pathological condition has subsided.

No one who has had much to do with conditions which are apt to cause root irritation or compression—spondylitis, spinal tumors,

fractures, and distortions of the spine, etc.—can doubt that the symptoms met with in the human subject are those of mechanical interference with the functions of the nerve roots. That such neural symptoms follow or accompany general infections of unknown origin, pneumococcus and gonococcus infections cannot be questioned. The literature contains numerous examples of such conditions. In all these cases, and in a considerable number which I have seen myself, the joint findings clinically and postmortem are all analogous to those in the dog; and though, except in a few instances, the actual spinal conditions have not as yet been demonstrated, I think it fair to assume that, inasmuch as the joint conditions are more or less perfectly analogous, the spinal conditions must be analogous as well.

Hence, as the neural symptoms in man are those of mechanical root compression and irritation, and as the pathological change following experimental streptococcus infection in the dog correspond exactly to one which would cause such a mechanical compression and such symptoms in man, I think the evidence that the pathological conditions in man and the dog are analogous is fairly conclusive.

I do not, however, mean to imply that all cases of spondylitis or polyarthritis which are associated with neural symptoms are streptococcus infections. All the microörganisms which cause nonsuppurative inflammation in man induce analogous changes in the bones, the joints, and the peri- and para-articular structures, and, as a consequence, may induce similar pathological and mechanical conditions in or near the spine. That a hemolytic streptococcus can cause spinal lesions with or without neural lesions is certain, for we have had such cases in which the microörganism was isolated from the blood under observation.

Whether all conditions associated with neural changes are infective is another question, and one more difficult, at the present time, to answer without at least some hesitation. In the cases with definite acute onset, temperature and general constitutional reaction, etc., it may, in the light of our present knowledge, be assumed that the cause is an infection. In the cases seen after the initial symptoms have subsided, however, the history given by the patient, which, as I have found to my cost, is nearly always unreliable, might lead one to believe that the disease is one with an insidious and progressive course, without definite onset or general reaction—one, in fact, due to some constitutional anomaly. When, however, the patient's subjective impressions are disregarded, the facts do not lend themselves to this interpretation. In the first place the actual changes, clinical and anatomical, in the joints are those of an inflammatory condition which, in a large proportion of the cases, no matter how chronic the course is self-limited. Moreover, the objective symptoms exactly correspond to those in cases of undoubted infec-

tion. Furthermore, it must be remembered that the stage of general infection in these cases may be extremely short, and the general reaction not only mild but evanescent.

It has been shown by a number of experimenters that the microorganisms injected, disappear from the blood in a remarkably short time. In Koch's and in my own experiments after a very short period of illness practically all the animals showed no general symptoms, although the pathological condition in the skeleton, etc., continued to progress. Hence, the presumption is that, in animals at any rate, the skeletal lesions are local in these cases, causing no general symptoms after the microörganisms have disappeared the blood and the toxemia caused by the initial invasion has subsided.

It is not unreasonable to assume that similar or analogous conditions occur in the human subject. In a large number of undoubted infections the initial disturbance is mild and of short duration, and may escape an unobserving patient entirely. As a matter of fact, I have known patients to have temperature as high as 103° without feeling at all feverish or ill. Under such circumstances it is not at all unlikely that in many cases the initial disturbance is so mild and evanescent, or the patient so unobserving, that these symptoms are overlooked, and thus the condition may be mistaken for a chronic constitutional malady.

Conclusions. Clinically, the neural symptoms associated with polyarthritis and spondylitis are those of moderate radicular or spinal irritation or compression. The variation in the symptoms can be fully accounted for by variations in the onset, the location, the intensity, and the course pursued by the pathological process causing the periradicular changes. Experimentally it has been shown that the vertebral changes which are induced by inoculating dogs with streptococcus are similar to those in the skeleton elsewhere. These changes are endosteal and subperiosteal inflammation, concomittant with a sterile intra-, peri-, and para-articular exudation. In the spine this exudate involved the epidural space and the vertebral notches; it was of such a nature that it must perforce have caused root or spinal irritation or compression. In some cases the findings lead me to conclude that the exudate is finally absorbed; in others, however, there could be no doubt that the exudate was followed by permanent connective-tissue changes.

These changes exactly correspond to a condition which in the human subject would lead to the neurological symptoms we have shown to exist in cases of polyarthritis and spondylitis.

As the spinal lesions in the dog are exactly the same as the peripheral joint lesions, and as peripheral joint lesions in the dog and man are absolutely analogous; and as we have no reason to believe that the bones and periarticular structures of the spine in man react differently to deleterious influences than those of the

skeleton generally, we must assume that the vertebral and epispinal morbid conditions in man are also analogous to those we have been able to demonstrate in the dog.

Hence, when the neurological symptoms here described are associated with arthritis it must be concluded that the spinal column is involved in the morbid process, and that the vertebral changes consisting of endosteal and subperiosteal inflammation have lead to epidural and perispinal exudation, causing root or slight spinal compression, which may or may not be permanent.

It therefore follows that the neural symptoms we have described as existing in the arthritis conditions are due to epidural or peri-epidural exudations, and the differences in the distribution, intensity, and permanence depend upon the distribution, the intensity, and the sequelæ of the epidural and perispinal process.

All these conditions are in all probability due to infection. The infection is not due to a specific microörganism, but may be caused by any organism which will produce non-suppurative inflammation in the bones and joints. The presence of nerve symptoms in some cases of polyarthritis or spondylitis, and their absence in others, must be ascribed to differences in the location and not to differences in the morbid condition which caused the spondylitis or polyarthritis. With the demonstration of these data, and assuming that my conclusions are correct, the significance of a number of perplexing symptoms occurring in the chronic deforming arthritides becomes evident. In the first place the much debated question of the neural origin of the chronic deforming arthritis is more or less definitely answered. It is certain, at any rate, that in the majority of cases the neural symptoms are due to mechanical disturbances in the spinal canal and that these mechanical disturbances are secondary to skeletal conditions. It therefore becomes unnecessary to classify the spondylitides according to presence or absence of neural symptoms, the mode of progression, or the involvement of the ribs and joints of the extremities. Whether these structures are involved or not is simply an accident of localization, and does not depend upon peculiarities or essential differences in the etiology or the pathogenesis of the morbid process.

It is then no longer necessary to specify by name the type of spondylitis, Bechterew, Strümpel, P. Maire, etc.; these conditions are not essentially different; they are all simple variations in the location of some inflammatory condition which, like all inflammatory conditions, may be acute or chronic, transient or progressive, with or without permanent damage to the tissues involved.

Moreover, if my deductions are correct, the reason why so many cases of polyarthritis present muscular atrophy and akroparesthesias in the early stages or even in the pre-articular stages becomes evident. In such cases, no doubt, the epidural surfaces of the vertebræ are involved before the peripheral articulations.

Upon these grounds, too, the origin and pathogenesis of those forms of chronic deforming arthritis in which the inflammatory joint changes are associated with gradually increasing weakness, trophic skin changes (edema, decubitus, ulceration, etc.) become clear. In such cases, so perplexing to the clinician, the joint changes point definitely to an inflammatory condition while the absence of temperature, the hyperesthesia, the spasticity, exaggerated reflexes, fibrillar contractions, increasing weakness, the neurotic edema, the hyperidrosis, the cold extremities, and the low blood-pressure lead one to suspect a neural condition combined with or secondary to an internal secretory anomaly. It is only when one has seen and closely observed such cases for years that one becomes aware of the fact that the joint and bone condition which was first inflammatory later becomes stationary and quiescent, and that the mechanically induced neural changes are in a large measure responsible for the pitiable condition of these patients. So in the case of which illustrations are here shown (Fig. 2). The patient has absolutely no signs of progressive joint disease; his extremities, though somewhat deformed, can be passively moved, and he has some active, painless motion in the upper extremities; but he is unable voluntarily to move the lower extremity at all, and must be lifted from the bed into a chair, etc. He has no pain and his symptoms in no way differ from those due to moderate mechanical radicular or spinal compression. In the beginning the symptoms were entirely articular and the disease ran the course common to all subacute and chronic arthritic inflammations. Such cases are not then, as has been supposed, primarily neural, for the articular symptoms may precede the apparently progressive neurological condition. The nerve phenomena are secondary to the skeletal conditions.

These facts are also important from a prognostic and therapeutic stand-point. It is evident that the patients with long-continued neural phenomena are not amenable to mechanical and surgical treatment, and these neural phenomena, unless they disappear early in the disease, are permanent. Hence, the prognosis in cases with well-developed and long-continued symptoms of radicular irritation or compression is unfavorable; while in the cases with marked joint involvement without nerve changes there is always a chance of improvement.

I wish to thank Dr. Noble, of the bacteriological department of the Carnegie Laboratory, for the bacteria used in my experiments. I can but inadequately express my thanks to Dr. Symmers, of the pathological department of the Carnegie Laboratory. It is entirely due to his kindness in supplying me with space and material that I was enabled to carry on this work.

The photomicrographs were made for me by Mr. Busse, of the College of Physicians and Surgeons.

LITERATURE.

Achard et Leopold, Levi. Atrophie des centres nerveux un cas d'atrophie musculaire et osseuse d'origine articulaire, Nouv. Iconongr. de la Salpêtr., 1898, xi, 262.

Amaral, E. do. Arthropathies blennorrhagiques, formes graves avec amyotrophie, Thèse de Paris, 1891.

Bazy. De l'atrophie musculaire comme cause de douleurs articulaires, Progres méd., 1889, xvii, Nr. 12.

v. Bechterew. Steifigkeit der Wirbelsaule und ihre Verkrummueng als Besondere Erkrankungsform, Neurol. Centralbl., 1893, 426.

v. Bechterew. Von der Verwachsing oder Steifigkeit der Wirbelsaule, Deutsch. Ztschr. f. Nervenh., 1897, xi, 327.

v. Bechterew. Ueber ankylosirende Entzuendung der Wirbelsaule und der grossen Extremitatengelenke, Deutsch. Ztschr. f. Nervenh., 1899, xv, 37.

v. Bechterew. Neue Beobachtungen und pathologisch-anatomische Untersuchungen über Steifigkeit der Wirbelsaule, Deutsch. Ztschr. f. Nervenh., 1899, xv, 45.

Berguiem. De l'atrophie du membre abdominal dans la coxalgie, Thèse, Paris, 1877.

Block. Zur Kenntnis der gonorrhoischen Gelenkund Nervenerkrankungen, Arch. f. Dermat. u. Syph., 1899, xlviii, 349.

Brisson. Étude sur la sciatique blennorrhagique, Thèse, Paris, 1883.

Charcot. Sur l'atrophie musculaire consecutive au rheumatisms articulaire chronique, Progres. méd., 1882, Nr. 25.

Charcot. Sur l'atrophie musculaire, qui succede a certaines lesions articulaires, Progres. méd., 1882, 377–397. Leçons de mardi, 1888, 505. Amyotrophies spinale reflexes d'origine abarticulaire, Progres. méd., 1893, 225.

Charcot. Sur l'atrophie musculaire qui succede a certaines lesions articulaire chronique, Progres méd., 1882, Nr. 25.

Chavrier et Fevrier. Manifestations spinales d. l. blennorrhagie, Revue de médecine, 1888, viii, 1020.

Clinch. The arthropathic dystrophies, Brit. Med. Jour., 1898, ii, 1925.

Cornillon, S. Amyotrophies consecutives a duex acces de goutte simulant l'atrophie muscul, progressive, Progres méd., 1883, Nr. 21.

Curschmann. Muskelveraenderungen bei Arthritis deformans, Bericht der medicinischen Gesellschaft zu Leipzig, 1859.

Damsch, O. Ueber chronische ankylosirende Entzuendung der Wirbelsaule und der Hueftgelenke (Strümpell), Ztschr. f. klin. Med., 1899, xxxvii, 471.

Dercum. A Case of Arthritic Muscular Atrophy of Gonorrheal Origin, Med. News, 1888, ii, 727.

Desnos, Joffroy et Pinard. Sur un cas d'atrophie musculaire des quatre membre, a evolution tres rapide, survenue pendant la grossesse et consecuitivement a des vomissements incoercibles, Bull. de l'acad., 1889, 3, sér xxi, p. 44, und Union méd., 1889, Nr. 12 u. 14.

Dufour. Sur la meningomyelite blennorrhagique, Thèse de Paris, 1889.

Engel-Reimers. Beitrage zur Kenntnis der gonorrhoischen Nerven- und Rüchenmarkserkrankungen, Jahrb. der Hamburger Staatskrankenanstalten 11, 1890, erschienen, 1892, 409.

Eulenburg. Ueber puerperale Neuritis und Polyneuritis, Deutsch. med. Wchnschr. 1895, 118–140.

Eulenburg. Ueber gonorrhoische Nervenerkrankungen, Deutsch. med. Wchnschr., 1900, 686.

Fournier. Blennorrhag., arthropathie deformante et amyotrophique, Ann. de Dermat. et de syph., 1899, No. 1.

Fraenkel, E. Ueber Erkrankungen des roten Knochenmarkes, besonders der Wirbel und Rippen, bei akuten infektionskrankheiten, Mitteil. a. d. Granzgeb., vol. xii.

Freud. Akute multiple Neuritis, Wien. med. Wchnschr., 1886, 168.

Frohner. Acute degenerative Muskelatrophie der Rucken- und Croupenmusculatur bei einem Vollblutpferde im Anschluh an das Abwerfen, Monatsschr. f. pratische Thierheilkunde, 1899, x, 354.

Gubler, A. De la paralysie amyotrophique consecutive aux maladies aigues, Mém. de la Soc. de la Biol., 1861, 39.

Gubler. Muscular atrophy following acute diseases, Brit. Med. Jour., February 22, 1862.

Hayem et Parmentier. Contributions a l'etude des manifestations spinales de la blennorrhagie, Revue de méd., 1888, viii, 433.

Heiligenthal. Die chronisch Steifigkeit der Wirbelsaule und die Spondylose rhizomelique, Centralbl. f. d. Grenzgeb. d. Med. u. Chir., 1900, iii, ii, 54, 86, 134, 181.

Hoffmann, Aug. Ueber chronische Steifigkeit der Wirbelsaule, Deutsch. Ztschr. f. Nervenh., 1899, xv, 28.

Jacoby, W. G. Neurotic Affections Accompanying Joint Lesions, Boston Med. and Surg. Jour., 1884, 10.

Jaksch. Ein Fall von polyarthritischer Erkrankung der Halswirbelsaule, Prag. med. Wchnschr., 1900, 37, 52, 63, 75.

Kahane. Ueber Neuromusculaire Erkrankung bei Polyarthritis rheumatica, Centralbl. f. klin. Med., 1892, xiii, 1041.

Kalinderu. Ueber die spinalen Komplikationen der Gonorrhoe, Klin ther., Wchnschr., Wien, 1899, 1209.

Kast. Beitrage zur Lehre von der Neuritis (Vortage, auf der Wandervers. sw. d. Neurologen), Arch. f. Psychiat., 1881, xii, 266.

Kast. Ueber acute einfache Muskelatrophie xii, Wanderversammlung deutscher Neurologen und Irrenarzte, June, 1887 zu Strassburg, Deutsch. med. Wchnschr., 1887, 583.

Leri, A. La spondylose rhizomelique, Revue de méd., 1899, xix, 597, 691, 801.

Levi et Follet. Myoclonie et Spondylose rhizomelique, Revue neurolog., 1900, 1111.

Magnus-Levy, A. Ueber die chronische Steifigkeit der Wirbelsaule, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1902, ix, 626.

Marie, P. Sur la spondylose rhizomelique, Revue de méd., 1898, 285.

Marie, P. Rhumatisme chronique infectieux et rhumatisme chronique arthritique, Leçons de clinique médicale, 1893.

Möbius. Ueber Neuritis peurperalis, München. med. Wchnschr., 1887, 153; 1890, 247; 1892, 799.

Müller, C. F. Ein Fall von multipler Neuritis, Arch. f. Psychiat., 1882, xiv, 669.

Nürnberger. Ein Fall von beiderseitiger Lähmung der Schulterblattmuskeln im Anschluss an akute Gonorrhoe, Inaug. Diss., Erlangen, 1894.

Oudin. Contribution a l'etude des arthropathies musculaires d'origine blennorrhagique, Ann. de dermat. et de syph., 1892, 856.

Pitres et Vaillard. Nevrites peripheriques dans le rhumatisme chronique, Revue de méd., 1887, vii, 456.

Raymond, F. Arthropathies multiple et atrophie musculaire generalisee consecutive, en rapport probable avec une infection blennorrhagique, Gazette médicale de Paris, 1891, No. 1.

Raymond, Paul. Les complications nerveuses de la blennorrhagie, Gaz. des hôp., 1891, 103.

Remak. Ein Fall von generalisirter Neuritis, etc. (Berl. Ges. f. Psych. u. Nerv., 1885), Neurol. Centralbl., iv, 313.

Revillout, V. Atrophie Musculaire consecutive a un rhumatisme articulaire chronique, Gaz. des hôp., 1878, No. 90, p. 713.

Robertson, A. Patient with Rheumatic Muscular Atrophy, Glasgow Med. Jour., 1894, 448.

Strümpell, A. Ueber Muskelatrophie bei Gelenkleiden und über atrophische Muskellahmung nach Ablauf des acuten Gelenkrheumatismus, München. med. Wchnschr., 1888, 211.

Valtat, E. De l'atrophie musculaire dans le cours des maladies des articulations, Arch. gén. de méd., 1877, ii, 159, 321.

A STUDY OF THE INVOLVEMENT OF THE BONES AND JOINTS IN EARLY SYPHILIS.

By Udo J. Wile, A.B., M.D.,

PROFESSOR OF DERMATOLOGY AND SYPHILOLOGY, UNIVERSITY OF MICHIGAN, DEPARTMENT OF MEDICINE AND SURGERY,

AND

Francis E. Senear, B.S., M.D.,

INSTRUCTOR IN DERMATOLOGY AND SYPHILOLOGY, UNIVERSITY OF MICHIGAN, DEPARTMENT OF MEDICINE AND SURGERY, ANN ARBOR, MICHIGAN.

The conception that syphilis in the early weeks and months of the infection attacks for the most part the superficial structures, and that the severe visceropathies and syphilitic disease of the bones and joints belong rather to the group known as the late sequelæ, is without doubt due to the fact that there has been little opportunity for studying the disease in its incipiency, as is possible with other diseases. It is only within very recent time that the hospital bed has become available for the freshly infected syphilitic. With the increased facilities for study of the disease early in its course it has become more and more apparent that all of the deeper structures are affected early in the course of the disease.

During the past four years we have been enabled at our University Hospital clinic to give particular attention to such phases of early syphilis as have not been previously studied. In all of our cases we have paid particular attention to the involvement of the nervous system, general health of the individual, the question of loss of weight, the involvement of the spleen and liver, and the involvement of the bony structures. Those phases dealing with the spleen and nervous system, together with such data as bear upon them, have been made the subject of a previous communication.[1]

That the bony structures, including also the articulations, are involved as late or so-called tertiary sequelæ is of course well-known. The occurrence of various arthropathies and bone lesions form a not inconsiderable part of the pathology of these structures. The same holds true of such involvement in so-called hereditary syphilis. A surprisingly small literature, however, exists dealing with the involvement of the bones and joints as part of the early manifestations of syphilitic infection.

[1] Wile and Elliott, A Study of Splenic Enlargement in Early Syphilis, Am. Jour. Med. Sc., 1915, cl, 512. Wile and Stokes, A Study of the Spinal Fluid, with Reference to Involvement of the Nervous System in Secondary Syphilis, Jour. Cutan. Dis., September, 1914, p. 607. Wile and Stokes, Involvement of the Nervous System during the Primary Stage of Syphilis, Jour. Am. Med. Assn., 1915, lxiv, 979. Wile and Stokes, Further Studies on the Spinal Fluid, with Reference to the Involvement of the Nervous System in Early Syphilis, Jour. Am. Med. Assn., 1915, lxiv, 1465.

We have studied during the past two years, with particular reference to early bone and joint involvement, 165 cases of syphilis in the primary and secondary periods. In all cases the long bones were carefully palpated and percussed for tenderness, and a careful note was made on the subjective symptoms pertaining to the bone and joint involvement, and all of the joints were carefully examined for objective lesions and functional impairment. In a few cases in which objective pathology was noted the roentgen-ray was also used. As in our previous communications we have attempted to show the possible relationship between the involvement of the various symptoms and later to demonstrate if there existed any predilection in the cases infected, for one or more particular systems. For this reason, in each case, parallel tables have been prepared, noting in each case the type and extent of the cutaneous lesions, the involvement of the nervous system, and the involvement of the general health. In all 60 cases of the 165 were found to have symptoms of objective findings referable to the pathology of the osseous system.

General Health. Of the 60 cases in which bone or joint involvement was found, 36 showed some definite constitutional disturbance due to their syphilis. Thus in 18 cases the general health was severely affected, as attested by severe anemia, debility, and a great loss of weight. Eight cases showed a mild involvement of the general health disturbance, the loss of weight, anemia, and debility being less marked, although the patient was definitely ill. The remaining 10 cases showed only a slight loss of weight and a mild degree of anorexia. The 24 remaining cases were entirely devoid of constitutional symptoms. Thus of the 60 cases in which the bone and joints were involved, 60 per cent. of the skeletal involvement was found associated with general health disturbance.

Type of Eruption. The analysis of the eruptive phenomena associated with bone involvement showed no apparent relation between the two to exist. All types of syphilides in about an equal proportion were found to exist with the bone manifestations.

Involvement of the Nervous System. In 31 of the 60 positive cases in our series careful neurological examination was made. Of these, 14 gave positive findings of the spinal fluid, together with associated neurological findings, while 17 were found to be uninvolved. Forty-five per cent., therefore, of the cases in which bone and joint involvement was present were cases also of neural syphilis. A previous investigation of all cases of secondary syphilis in this clinic with reference to early involvement of the central nervous system showed 70 per cent. of the cases involved. The marked difference between the figures in all cases of secondary syphilis and those which showed bone and joint involvement suggests an inverse ratio between the involvement of these two systems.

SPLEEN. In about 30 per cent. of those cases in which the bones and joints were involved, definite splenic enlargement could be demonstrated.

With regard to the development of the bone and joint manifestations, it is interesting to note that of the 60 cases, only 3 could possibly have been associated with definite traumata. In 57 the involvement seemed to be entirely spontaneous. This is in striking contrast to the development of the bone and joint manifestation in the later stages of the disease, in which the element of trauma is an all-important factor in the development of the pathology.

In considering the influence of early and efficient treatment upon the development of bone and joint syphilis it is interesting to note that in our series 41 cases had received absolutely no treatment before entering the clinic; of the remaining 19, 6 had received salvarsan and mercury combined, and only 2 had had intense mercurial treatment. Of the remainder the treatment had been desultory. In other words the vast majority had received little or indifferent treatment, and only one or two had received efficient treatment.

The symptomatology of the cases is as follows: 27 cases showed involvement of the bones only; in 21 the joints were affected independently; in the remaining 12 cases the bones and joints were involved together.

PAIN. In all but one case in which the bones were involved more or less pain was present. This varied from a dull intermittent pain described by some patients as a "dragging sensation" to the most exquisite, sharply localized tenderness. For the most part the pain was nocturnal in character and was relieved somewhat by exercise.

It required in many cases the most careful examination of the long bones to determine small foci of localized tenderness. The points of maximum tenderness were in some cases so small that unless each portion of the bone was palpated one could easily have missed them. Particularly is this true of such cases in which the pain was not spontaneous but one brought on by pressure. In not a few cases in which pain was complained of in the long bones it was impossible by methods of palpation or by the most careful examination to determine any localization of the pain. Indeed, the patients complained of bone pains without themselves being able to localize any point of tenderness. The character of such pain was rather dull, and in a few cases the patients described it as deep. We are inclined to believe that such pain was distinctly medullary, and in our experience such pain is not so readily amenable to treatment as is that of the periostitis or other more superficial points of tenderness, marked on the surface of the bone. A few patients who complained of pain in the muscles were found, on examination,

actually to have points of tenderness along the periosteum or actual periosteal nodes.

Objectively, periostitis was the most frequent clinical finding. The tibia was thus involved in 8 cases examined and the sternum was next in frequency, the skull and ribs next. The clavicle was the only site in which the periosteal node was found to be absolutely painless.

JOINTS. Arthralgia was the most common finding referable to the articulations. It was present in 17 of 21 cases studied. The pain, as in the cases of the bones, was for the most part nocturnal, and was also relieved by exercise. In the order of frequency the ankles, the metatarsophalangeal joints and the elbows were affected, and in one case the elbow and shoulder-joint of the same side were affected. Pressure on such joints was always followed by sharp pain. In all of the arthropathies only 5 cases were shown to have objective signs. In one case the knee showed a distinct, symmetrical swelling, in a second the hip-joint, in a third the shoulders were the sites of visible tumescence. Definite hydrarthrosis was present in two cases, both the knees being affected in one and both ankles in the second. In one case there was marked swelling of both knees without any subjective disturbance. In all of the cases studied prompt amelioration took place as soon as efficient treatment had been begun.

The periosteal node and early arthralgia may be looked upon as relatively superficial syphilides and rapidly amenable to treatment. The involvement of the medulla of the bone, however, must be regarded much in the same light as a severe visceral syphilide comparable, perhaps to the involvement of the spleen. It is not at all unlikely that spirochetal "rests" occur in the marrow of the long bones from such early implantation. Such rests may well serve as distributing foci of the later sequelæ, not only in the bones themselves, but possibly such foci serve as depots from which under the influence of either trauma or other factors, the circulation is recharged with spirochetes.

From our studies we conclude that the skeletal structures offer no exceptional barrier to objective or subjective involvement in early syphilis. The apparent and relative infrequency of their occurrence is easily found in the fact that ambulatory cases of syphilis are seldom examined with regard to the bony structures.

The rapidity with which the more superficial lesions disappear under appropriate therapeutic measures justifies the conclusion that such involvement adds nothing to the seriousness of the early symptom-complex.

Those cases, however, in which deep, non-localized pain occurs, without objective findings, probably constitute more serious involvement. They require more vigorous treatment for their

disappearance, and must be regarded as an invasion of the bone marrow itself.

The frequent association of the osseous system with involvement of all the other systems would seem to indicate that there is no justification for assuming an osteotropic strain of the infecting organism.

From the stand-point of differential diagnosis the early syphilitic bone and joint manifestations offer no great difficulties. The most important diagnostic features seem to be the presence of pain during the periods of repose.

A CASE OF MULTIPLE MYELOMATA, WITH A DISCUSSION AS TO ITS NATURE AND ORIGIN.*

By B. M. Vance, M.D.,

PATHOLOGICAL LABORATORY, BELLEVUE HOSPITAL, NEW YORK CITY.

(From the Department of Bellevue and Allied Hospitals Charles Norris, M.D., Director.)

INTRODUCTION.

V. Rustizky,[61] in 1876, was the first to apply the term "multiple myelomata" to a case of primary multiple tumors of the skeleton, which he believed arose from the blood-forming cells of the bone marrow. Since that time many different types of multiple bone-marrow tumors have been described under this name of "multiple myelomata," and the condition is now recognized as a definite pathological entity. There is still uncertainty and lack of unanimity in regard to the true classification of these tumors, although the majority of observers are agreed that they are derived from the blood-forming cells of the bone marrow and are related to the primary diseases of the lymphatic-hemapoietic apparatus.

CLINICAL AND PATHOLOGICAL FEATURES OF MULTIPLE MYELOMATA.

The clinical and pathological pictures of the cases of multiple myelomata which have been described are very similar. The disease is one of adult life, over 60 per cent. of the cases occurring between the ages of forty and sixty; 26 per cent. over sixty years,

* I am greatly indebted to Dr. Charles Norris, at whose suggestion this work was undertaken, and to Drs. Van Horne Norris and William K. Draper, through whose courtesy the publication of the clinical notes on the case was made possible.

and only in a very few cases was the age below forty; 76 per cent. of the cases occurred in men and 24 per cent. in women of the poorer classes. The cases described by Nothnagel[53] and Israel[36] were both young males† of twenty-four and twenty-six years of age respectively, but we have reason to believe that these were not multiple myelomata.

The cases of multiple myelomata all show involvement of the skeleton by tumors which arise primarily from the bone marrow. The bones usually involved are those of the axial skeleton, vertebræ, sternum, and ribs, less often the skull, and the bones of the extremities. The neoplasm, for the most part, has been described as a soft, gelatinous, vascular growth, red or reddish gray in color, in which dark red hemorrhagic areas are common. In other cases the color has been raspberry red, reddish violet, brownish red, yellow, gray, and white. The tumor is confined to the bones, and in only a few instances has it been described in extraskeletal situations. It entirely replaces the normal red bone marrow in the involved areas, and has a corroding action upon the bony tissues themselves. Occasionally it has occurred as circumscribed grayish nodules in the midst of the normal marrow, causing only slight destruction of the osseous tissue.

The involvement of the skeleton renders the bones fragile and gives rise to many characteristic deformities. The vertebral column most often shows an angular kyphosis, due to the destruction of the vertebral bodies in the dorsal and lumbar regions. The sternum, also, presents various grades of deformity, from a simple bowing to an S-shaped curve, which is most marked when accompanied by a kyphosis. Tumor masses of soft consistency may project from either the anterior or posterior surfaces of the sternum, and in the case of Lubarsch,[45] such a mass had apparently been separated from the posterior surface of the sternum and lay free in the tissues of the mediastinum. The ribs usually show fusiform swellings near their costovertebral and costochondral junctions. Occasionally tumor masses have been found in the bones of the skull, pelvis, and the extremities of the long bones, but have caused no characteristic deformities in these situations. Spontaneous fractures are common and occur most frequently in the ribs and less often in the bones of the extremities.

Prominent symptoms of the disease are pain and tenderness to pressure, which are referred, as a rule, to the bones most frequently involved, namely, the ribs, the bones of the extremities, and the vertebræ. The pain is persistent and deep-seated, and becomes more intense whenever the part is moved, either actively or pas-

† Schridde in Aschoff's Lehrbuch, 1913 edition, shows an illustration of a femur of a twenty-year-old male which he diagnoses as a "multiple erythromyeloblastome." There is nothing in the text to indicate that the tumor belongs to the multiple myelomata.

sively. When the involvement is at all extensive, the pain may be so severe as to confine the patient to bed. The patients also suffer from neuralgic pains, referred to the internal viscera, which Parkes Weber[90] believes are caused by compression exerted by the kyphotic vertebral column on the posterior nerve roots in the intervertebral foramina. Some cases, especially in the later stages of the disease, develop a severe secondary anemia, and become markedly emaciated. The number of erythrocytes varies from 3,000,000 to 4,000,000, while the hemoglobin estimation is from 50 to 80 per cent. The leukocyte count is almost always low, varying from 7000 to 15,000, while the differential count shows the normal variations. In no case have any myelocytes been found in the circulating blood. There were many nucleated red cells in the case of Jochmann and Schumm,[38] while in Ellinger's case[19] the anemia was the dominating feature of the disease, and was of the primary pernicious type.

The patients in several instances have developed symptoms of a myelitis transversa with paraplegia, incontinence of urine and feces, etc. This has been found at autopsy to be due to pressure exerted on the spinal cord by the deformed vertebral column.

Other symptoms have been recorded, but these are not typical of multiple myelomata, and are rather due to general exhaustion or some complication. The disease usually runs a chronic course of from six months to two years. In many cases lobar pneumonia is the terminal condition.

A few cases of multiple myelomata have shown tumor tissue, similar to the neoplasm in the bones, present in other parts of the body, as in the left inguinal lymph nodes of the case of Scheele and Herxheimer;[63] in the iliac lymph nodes of the case of Charles and Sanguinetti;[13] in the liver of the case of Hoffmann;[34] in the ovaries of the case of Herrick and Hektoen;[30] on the cricoid cartilage of the case of v. Verebely.[83] The significance of these extraskeletal tumor growths will be discussed later.

There are no secondary pathological changes which can be considered characteristic of multiple myelomata. A few cases have been reported, in which amyloid changes were present in some of the viscera (cases of Heuter[35]); Parkes Weber;[89] H. Weber;[88] O. Pertik.[57] In three cases, those of Bender,[7] Scheele and Herxheimer,[63] Tschistowitsch and Kolessnikoff,[81] deposits of calcium salts were found in the viscera. In the last-named case the deposits resembled the "chalk metastases of Virchow," and were present in the lungs, kidneys, spleen, stomach, heart muscle, and liver.

Another phenomenon, which is observed very often in cases of multiple myelomata, is the presence of Bence-Jones protein in the urine. This is considered by some observers (Kahler,[40] Parkes Weber,[89] Moffat, and others) to be pathognomonic of the disease. Its significance will be discussed in another section.

THE MICROSCOPIC CHARACTERISTICS OF MULTIPLE MYELOMATA, WITH SPECIAL REFERENCE TO THE PLASMA CELL TUMORS.

While the clinical and pathological features of the cases of multiple myelomata are remarkably similar, a variety of types have been distinguished on the basis of the histological characteristics of the tumor cells. There is no doubt, however, that these cells, diverse as they are, are derivatives of the undifferentiated cell of the bone marrow or the myeloblast, which is the ancestor of both the leukocyte and the erythrocyte. The cells of the myelomata always resemble certain elements of normal marrow, and in several cases, such as the one of v. Verebely,[83] where the line of demarcation between normal marrow and tumor tissue was found to be slight, many tumor cells were found in the normal marrow.

The myelomata are composed of large spherical or polyhedral cells which lie without definite arrangement in a fine connective-tissue stroma, separated from each other by a formless ground substance. The stroma contains many thin-walled vessels, most of which are composed of only one layer of endothelial cells. Hemorrhages are prone to occur from the bursting of these vessels, in which case red blood corpuscles lie among the tumor cells. The neoplasm, however, may have a very poor vascular supply, though areas of necrosis are rare in any portion of the tumor. Bone is hardly ever found in the new growth because of the destructive or lytic action of the tumor cells. The cases of Bender,[7] Winkler,[95] Ellinger,[19] Jochmann and Schumm,[38] Scheele and Herxheimer,[63] v. Rustizky,[61] Permin[56]—case 1—showed many giant cells or osteoclasts, and it is possible that they may have contributed to the destruction of the bone.

Five different types of multiple myelomata have been distinguished in the literature on the basis of the morphology of the tumor cell. There is first of all the type which is composed of cells resembling the myeloblast. This is a large spherical cell about the size of a large lymphocyte with an abundant, non-granular, lightly basophilic cytoplasm and a large vesicular nucleus. The nuclei are either centrally or excentrically placed, stain weakly basophilic, and possess a fine filamentous chromatin network, in which lies the acidophilic nucleolus. Cases which belong to the group have been described by v. Rustizky,[61] McCallum,[46] Zinninger,[98] Vignard and Gallavardin,[85] Hart,[29] Permin,[56] Jellinek,[37] Tschistowitsch and Kolessnikoff,[81] Shennan[70] and others.

A second class are formed by those cases whose cells have the size and appearance of the ordinary small lymphocyte. This type was designated by the earlier observers as a lymphosarcoma or pseudoleukemia confined to the bones. Cases of this kind are described by Zahn,[97] Kahler,[40] Herrick and Hektoen,[30] Pertik,[57] Scheele and Herxheimer,[63] Ellinger,[19] Parkes Weber[90] and others.

A third group of multiple myelomata are composed of cells whose cytoplasm contains neutrophilic granules. These may be regularly distributed as in the normal neutrophilic myelocyte, or the cells may contain huge and irregularly shaped pigment clumps. Parkes Weber[89] considers that such cells are atypical derivatives of the neutrophilic myelocyte. Cases of this sort were described by Winkler,[95] Saltykow,[62] C. Sternberg,[74] Parkes Weber,[89] Lubarsch,[45] Herz.[32]

The fourth group is represented by the case of Ribbert,[59] in which the tumor cells differed from those of any other case of multiple myelomata, in that they contained hemoglobin, and thus resembled erythroblasts. He called the tumor an erythroblastoma, and claimed that all stages of the formation of the nucleated red blood cells were present in the tumor growth. Up to the present time no other case of this kind has been described in the literature.

The fifth group is known as the "plasmocytomata," and is composed of those cases whose cells were described as morphologically similar to the plasma cells of Unna and v. Marschalkó. This cell is irregularly oval in shape and about the size of a large lymphocyte. Its protoplasm takes a deep basophilic tint in its peripheral portion, but shows a clear space around the excentrically placed nucleus. The latter is vesicular in type, shows dark chromatin clumps arranged peripherally just within the nuclear membrane, and contains an intensely staining acidophilic nucleus. Cells of this definite morphology were first described by Unna in 1891, in sections of lupus, and called by him "plasma cells," from their supposed resemblance to the "plasma cells" described by Waldeyer in normal testicles.

Since that time plasma cells have been found in the normal intestinal submucosa, spleen, bone marrow, and lymphatic tissues, and in many inflammatory processes, especially of the tongue and kidney (acute interstitial nephritis of Councilman). Many observers have regarded the cell as inflammatory in nature, but they have been unable to determine its origin or mode of development. Unna looked upon the plasma cell as a product of the fixed connective-tissue cells. V. Marschalkó considered it a derivative of the small lymphocyte, basing his theory on the prevalence of plasma cells in inflammatory areas where lymphocytes were especially numerous. Marchand regarded the plasmocytes as descendants of the "klasmocytes," or the cells in the adventitial coat of the smaller blood-vessels. None of these theories are capable of proof.

Elements morphologically resembling plasma cells have been described as the tumor cells in a great variety of cases. These include a large number of small isolated tumors of the uvula and eyelids, and conditions which possess the pathological features of lymphomata, pseudoleukemias, or lymphatic leukemias (cases of Gluzinski and Reichenstein,[23] Ghon and Roman,[99] Maresch, Vogt,

and others). Many cases of multiple myelomata have been regarded as plasmocytomata, among which are those of Wright,[96] Christian,[14] Hoffman,[34] Berblinger,[8] Aschoff,[2] Parkes Weber and Ledingham,[91] v. Verebely,[83] Warstat.[87] These observers consider that the tumor cells are derived from the "plasma cells," in the bone marrow, and Berblinger[1], applying v. Marschalko's theory to multiple myelomata, suggests that they arise primarily from the bone-marrow lymphocyte.

The plasma cell, as a matter of fact, is purely a morphological entity and little is known concerning its origin, mode of development, or function. Cells, resembling it, have been described in inflammatory processes, and it is possible that they have a specific role in inflammation, which, however, is still poorly understood. There are, also, many tumor formations composed of cells of "plasma-cell" morphology, and their exact status is uncertain, because such neoplasms can only be classified on their morphological characteristics without regard to embryological considerations. It is especially misleading to speak of certain multiple myelomata as "plasma-cell tumors," not only because the relationship between the plasmocyte and myeloblast is so indefinite, but because many such plasmocytomata are composed of elements quite unlike the "plasma cell" of Unna and v. Marschalkó.

A few cases of multiple bone tumors have been described which resembled multiple myelomata in their clinical course and at autopsy, namely, Seegelken's chondrosarcoma,[68] Marckwald's endothelioma of the bones,[49] and the peculiar case of Devic and Beriel,[17] about which no positive statement was made. The microscopic examination of these cases showed that while the tumors sprang from the bone marrow they were not derived from the myeloid cells proper, and were consequently not multiple myelomata.

CASE.

The patient, George McK., aged fifty-four years, a window dresser by occupation, was admitted to the service of Dr. Draper, in the medical ward of the first division of Bellevue Hospital, January 26, 1912. Seven months before his admission he complained of pain in his neck and ribs. The pain was constant and dull in character, and was increased by motion. The symptoms gradually became more severe, and he was forced to take to bed about two months after the onset of the disease. His previous medical history and that of his family history was negligible.

On admission, physical examination showed a well-nourished but poorly developed man of late middle life, who lay quietly in bed, complaining of stiff neck and pain in the sides. The examination was otherwise negative. On January 29, 1912, an ill-defined tumor, tender to pressure, was discovered in the right anterior triangle of

the neck, and attached, apparently, to the bodies of the cervical vertebræ. It increased progressively in size, and by June had assumed the consistence of bone. The patient's condition from June to September improved to such an extent that he was allowed to walk around the wards, though still complaining of pain and stiffness in his neck.

FIG. 1.—Right arm and chest.

Physical examination on September 20, 1912, was as follows: The lambdoid suture of the skull was more prominent on the left side than on the right. The head was held forward with the chin slightly depressed. Rotation of the head was limited to 20 degrees to the right and 30 degrees to the left, because of the pain and physical obstruction. The manubrium sterni was prominent. The ribs were thickened at the costochondral articulations, but none showed crepitus or abnormal mobility. The thigh at the level of the greater trochanter was much larger on the left side than on the right. There was no tenderness or loss of motion in the back, but there was a slight kyphosis present, and the lumbar spines were

quite prominent. The general condition of the patient was hardly changed at all.

In October pain in the neck became much worse and the patient gradually grew weaker, so that he had to go to bed. He died October 26, 1912, seven months after admission, on the service of Dr. Norris, the duration of the disease having been fourteen months.

The radiographic examination on February 23 showed areas of rarefaction in the left clavicle, right humerus, right scapula, greater trochanter of the right femur, ribs, upper cervical vertebræ, and the small bones of the hands.

The blood examinations showed a slight secondary anemia. The examination on August 27 revealed erythrocytes, 5,200,000. Hemoglobin, 72 per cent.; leukocytes, 5000; polymorphonuclears, 73 per cent.; lymphocytes, 26 per cent.; transitionals, 1 per cent. No myelocytes or abnormal cells were found in the blood at any time.

January 27 the urine was clear, amber in color, specific gravity 1029, acid in reaction and without glucose, indican, or bile pigment. January 31 the Bence-Jones protein was found in the urine. It was found both early and late in the disease, and in very large amounts, forming a heavy, brownish, sticky, peptone-like mass adhering to the stirring rod. The substance had all the characteristics of the Bence-Jones protein.

Clinical Diagnosis. Multiple myelomata.

The autopsy was performed by Dr. Norris on October 26, within an hour of the patient's death.

The anatomical diagnosis was multiple myelomata, lobar pneumonia, double adhesive pleuritis, chronic congestion of the kidneys, parenchymatous hepatitis, suppurative otitis media, and sphenoiditis.

Body was that of an elderly male adult, 176 cm. in height, very pale and emaciated.

Lungs: The lungs were congested and edematous. The upper lobe of the right lung was consolidated, showing a lobar pneumonia in the stage of red hepatization. The pleural surfaces were everywhere firmly adherent to the chest wall by fibrous adhesions. The bronchi were normal. The bronchial lymph nodes were small and anthracotic.

Heart: The heart was normal in size. The valves were normal, except that one of the pulmonary cusps was very large and fenestrated, and the left and middle aortic cusps were adherent near their edges. The musculature was dark red in color and showed no fibrosis. The coronary arteries were normal. The upper part of the aorta was normal, but the lower part of the adbominal portion showed a commencing sclerosis.

Peritoneum: The peritoneum was normal, except for an adhesion between the duodenum and the gall-bladder.

Gastro-intestinal tract: Normal.

Liver: The liver weighed 1840 grams. It was dark red in color, and had a cloudy appearance on section. The gall-bladder was normal and distended by black tarry bile.

Spleen: The spleen weighed 100 grams. The capsule was normal. The splenic pulp was pale red in color, and showed many fibrous septa.

Suprarenals: Apparently normal.

FIG. 2.—Right hand.

Genito-urinary tract: The kidneys were large and congested, and weighed about 475 grams. They were firm. The capsule stripped off readily, leaving a smooth surface on which were a few small cysts. The cortex was thickened and its markings indistinct. The pelves, ureters, and urinary bladder were normal.

The prostate was enlarged, and in both lateral lobes were two large foci of increased firmness. There was a double hydrocele, the one on the left side being larger than the one on the right. The testicles and epididymes were normal.

Organs of the throat and neck: These were normal.

Head: The scalp, the meninges, and the brain were normal. The left middle ear was normal, while the right middle ear and sphenoidal sinuses contained a considerable amount of thin whitish pus.

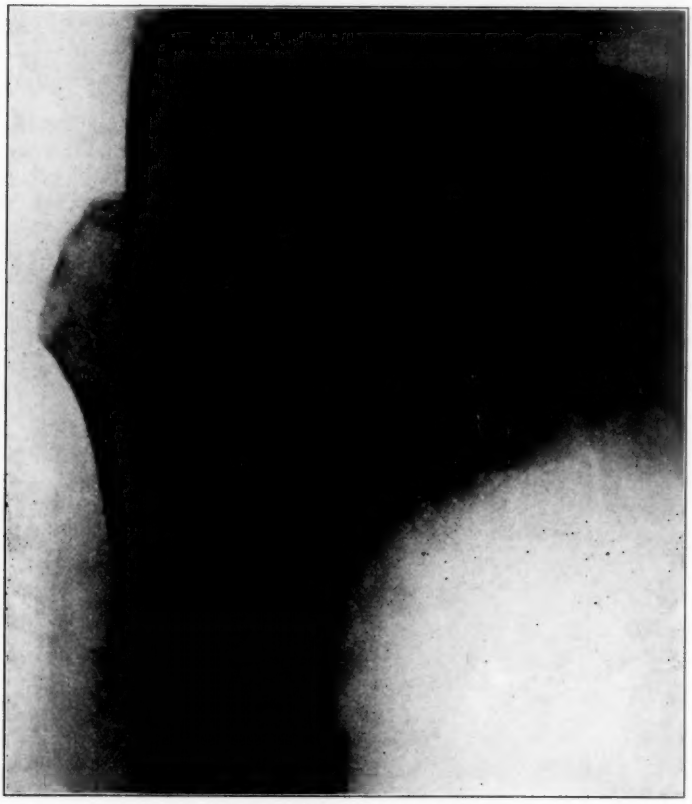


FIG. 3.—Right hip and pelvis.

Skeleton: The bones of the skeleton were extensively infiltrated by a neoplasm, yellowish white in color, in consistency like jelly, and homogeneous in appearance, resembling a rapidly growing round-cell sarcoma. The growth was in many places the seat of hemorrhages which gave it the dark red appearance of freshly clotted blood. The cancellous bone had entirely disappeared in the regions occupied by the neoplasm, and the periosteal layer also was thinned out by the growth.

The bodies of the cervical vertebræ were almost entirely replaced by the tumor tissue, and some of the intervertebral cartilaginous disks showed granular degeneration and softening. The tumor mass in the neck projected from the anterior surface of the bodies of the cervical vertebræ and infiltrated the adjacent soft tissues. It extended from the basilar portion of the occipital bone to the superior thoracic opening. A few of the dorsal and lumbar vertebræ were found to be infiltrated with tumor tissue, and there was a slight kyphosis present in the lumbar region. Thorough investigation of the vertebral column, however, was impossible.

Externally, the anterior portion of the chest wall was depressed, the ribs were bowed, and displayed numerous fusiform swellings composed of hemorrhagic tumor tissue, surrounded by periosteum. The largest of these swellings was about the size of a chicken's egg. They were situated near the costochondral junction and projected into the pleural cavity, carrying before them the thickened pleural membrane.

The sternum was everywhere infiltrated by hemorrhagic, neoplastic tissue, but, except for a marked increase in thickness, showed no special deformity. The lower end of the right femur contained a small red area of tumor formation, say 2 x 1 x 1 cm. The entire upper half of the right femur was infiltrated by soft, white tumor tissue, containing large, dark red hemorrhagic areas. The clavicles also showed focal areas of tumor infiltration. The other bones of the body were not examined at autopsy.

The neoplasm was entirely confined to the skeleton, and no tumor tissue was found in the other viscera. The tumors showed no tendency to infiltrate into the soft parts around the bones except in the anterior portion of the neck. The anatomical characteristics of the tumor indicated that it was a multiple primary neoplasm of the red bone marrow.

Microscopic Examination. The viscera, upon microscopic examination, showed but few noteworthy changes. Sections of the upper lobe of the right lung presented the typical picture of pneumonic consolidation. The rectus abdominalis muscle was the seat of a marked Zenker's degeneration.

The liver showed marked parenchymatous degeneration. The spleen contained a few focal necroses. The kidneys were the seat of a slight chronic parenchymatous nephritis and passive congestion. The left kidney contained a small fibroma situated in one of the pyramids. The other viscera were practically normal.

Pieces of the tumor were fixed in formalin, Orth's and Zenker's fluid. Absolute alcohol was not employed. The imbedding was in celloidin, and the sections were stained with hematoxylin and eosin, with Wright's stain, Jenner's stain, Unna's methyl-green pyronin stain, Ehrlich's triacid stain, Butterfield's[103] eosin-thionin stain, Mallory's anilin-blue connective-tissue stain and Mallory's

phosphotungstic acid hematoxylin. Smears were made from the fresh tumor tissue, but from them nothing was gained. The oxydase test was made by Prof. William G. McCallum, and was negative.

The sections of the tumor from the neck, the ribs, and the head of the femur were found to be similar in their microscopic structure. The stroma was composed of a very fine and quite cellular connective tissue, with a moderate number of delicate bloodvessels, which in some places consisted of a single layer of endothelial cells. The tumor cells lay closely packed, but separated in some places by an eosinophilic ground substance in the form of small globules. The sections taken from the hemorrhagic area showed numerous erythrocytes between the tumor cells. No tumor cells were found in the lumen of any of the bloodvessels.

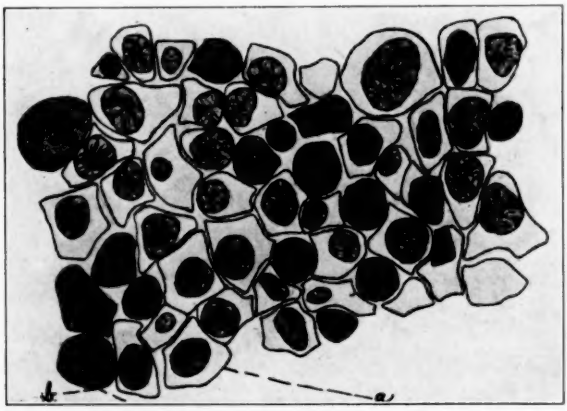


FIG. 4.—Drawing of a section from tumor in cervical vertebræ. (*a*) tumor cell of the myeloblast type; (*b*) tumor cell with pyknotic nucleus.

The tumor cells were of several types. The most numerous was a large spherical or polyhedral cell of slightly basophilic protoplasm, surrounding a large vesicular and excentrically placed nucleus. This nucleus contained several dark blue chromatin clumps, arranged against the nuclear membrane, a fine filamentous chromatin network, and an intensely staining acidophilic nucleolus. No granulations of any kind could be demonstrated in the cell protoplasm. This cell had the appearance, size, and general staining reactions of the ungranulated cell of the bone marrow, the common ancestor of the granulated myelocyte and the nucleated red cell.

Another type was a cell with a solid dark blue, pyknotic nucleus, excentrically placed, and an eosinophilic protoplasm, which at first, was held to be due to the presence of hemaglobin (Norris and Vance[52]). These cells varied in size from a small lymphocyte to that of the cell described with the basophilic protoplasm and vesicular

nucleus. They had a close resemblance to normal erythroblasts until it was found on high magnification that the protoplasm did not stain diffusely. The stain occurred in the form of irregular eosinophilic clumps, which were composed of small globules about the size of a nucleolus. In many cells, single globules of this type were found just outside the pyknotic nucleus, and surrounded by a clear space in the midst of the eosinophilic protoplasm.

Cells which appeared to be transitional forms between the above types were also seen. Their cytoplasm stained all gradations from a light basophilia to a complete eosinophilia. Their nuclei showed all intermediate stages from the vesicular type to that of complete pyknosis, while others displayed different varieties of karyorrhexis. The impression was given that there existed an active process of degeneration among the tumor cells.

SUMMARY OF CASE.

At autopsy there was found a multiple primary neoplasm of the bone marrow, extensively infiltrating the ribs, cervical vertebræ, clavicles, sternum, and femur. The tumor tissue caused destruction of the bone, wearing away the cortex to a thin layer and entirely replacing the cancellous bone. The neoplasm was confined to the osseous system, the viscera were not involved nor were the surrounding soft tissues infiltrated, except in the neck. The tumor was yellowish white in color, soft in consistency and homogeneous in appearance, resembling a rapidly growing round-celled sarcoma. The masses in the sternum and the head of the right femur showed extensive hemorrhages, which gave the neoplasm a dark red appearance like clotted blood.

On microscopic examination the tumor cells were found packed together in a stroma, consisting of very fine cellular connective tissue, delicate bloodvessels, a fine eosinophilic ground substance, and red blood cells whenever the section was taken from a hemorrhagic area.

It is plain that the tumor cells in this case all took their origin from the cells of the bone marrow. The large cell with the basophilic cytoplasm and the large vesicular nucleus was morphologically very similar to the myeloblast of the bone marrow. The cell with the irregularly staining eosinophilic protoplasm and pyknotic nucleus was not so easy to identify, though it was quite evident from the presence of transitional forms that it must have been derived from the myeloblast type. Its existence can be explained in two ways:

1. The neoplasm is an erythroblastoma, as described by Ribbert,[59] in which case the cell is a nucleated red cell and the process in the tumor is erythroblast formation. The objection to this theory is that the tumor elements with the pyknotic nuclei take the eosin stain irregularly and not diffusely, and are consequently not normal

erythroblasts. On the other hand, they may be regarded as an atypical form of the nucleated red cell in which the protoplasm manufactures hemoglobin in an abortive fashion. The substantiation of this theory depends on the demonstration of hemoglobin in the cytoplasm, and that was impossible from the material at our disposal in this case.

2. The neoplasm can be considered as a myeloblastoma, in which occur different stages of cell degeneration and disintegration. If we accept this theory we must regard the eosinophilic material in the cytoplasm as distinct from hemoglobin, because hemoglobin never occurs in a cell unless it is manufactured by the protoplasm or else acquired by the phagocytosis of normal erythrocytes. The first possibility would give the cells the dignity of erythroblasts, while the second view is not tenable in this case, because there is no phagocytosis present in the tumor. Christian[14] advanced the theory that the degenerating tumor cells have the power to imbibe the soluble hemoglobin in the tissues, but this idea is erroneous. Besides, degenerating protoplasm is invariably acidophilic, and the eosinophilia can be explained on the grounds of cell disintegration.

This case is not identical with any other case described in the literature, though it has many points of similarity with those described by Ribbert,[59] McCallum,[46] Wright,[96] Parkes Weber,[89] Christian,[14] Permin.[56] It is difficult to decide whether to classify the tumor as an erythroblastoma showing the formation of atypical erythroblasts, or as a myeloblastoma showing numerous cell degenerations. It is certain that the large cells with the vesicular nucleus are derived from the myeloblast of the bone marrow, but further differentiation is not possible because of our lack of knowledge concerning the significance of the other cell forms in the tumor.

A CONSIDERATION OF THE RELATIONSHIP OF THE MULTIPLE MYELOMATA TO THE DISEASES OF THE LYMPHATIC-HEMAPOIETIC APPARATUS.

A short review of bone-marrow formation is necessary for a comprehensive conception of the different primary affections of the lymphatic-hemapoietic apparatus.

Maximow described the migration of the undifferentiated star-shaped cells and newly formed bloodvessels from the perichondrium into the prebony cartilage as the beginning of blood formation in the skeleton. The star-shaped cells developed into two primary forms: (1) the fixed supporting cells which linked themselves together by long processes, and (2) the spherical "Wanderzellen" or myeloblasts. The bone marrow at this stage resembles lymphatic tissue so markedly that it is known as "lymphoid marrow." Later, the fixed supporting cells develop into the osteoblast, osteoclast, and the reticular cell of the marrow, while the myeloblasts become

differentiated into the various blood-forming elements, as the erythroblast, the granulated myelocytes, the small lymphocyte-like cells, and the megakaryocyte.

Now the morphology and genesis of the lymphoblasts, the "Wanderzellen" of lymphatic tissues, is very similar to that of the myeloblasts, but their future development is not, as the lymphoblast develops under normal conditions into a single cell form the small lymphocyte. However, it is a well-known fact that myeloid cells very often appear in lymphatic tissues in many pathological processes, such as the myelogenous leukemias and the severe anemias, and conversely lymphocytes occur in the bone marrow in lymphatic leukemias and pseudoleukemias. The consensus of opinion is that such aberrant elements develop from cells normally present in these situations, which suggests that the myeloblast and lymphoblast are closely related though not absolutely identical.

The above embryological considerations offer a basis of classification and a reasonable explanation for the variety of primary neoplasms which occur in the bone marrow. They are divided into two main groups. The first group take their origin from the fixed supporting cell of the embryonic bone marrow, and include the benign connective-tissue tumors, the endotheliomata, and the ordinary malignant sarcomata. The second group are derived from the primary mesenchymal "Wanderzellen," and are classified under the title of "Primary Diseases of the Lymphatic-hemapoietic Apparatus." These tumors are peculiar, pathologically, in that the neoplastic tissue pervades the body as a diffuse infiltration, or in the form of discrete nodules; but it is only found in situations where lymphoid and myeloid tissues are normally present. The tumors are primary hyperplasias of some single derivative, or group of derivatives, of the lymphoblast or myeloblast at each separate situation rather than metastases in the sense of the word as applied to malignant sarcomata. The tumor cells can also be demonstrated in the circulating blood in some forms, namely, the leukemias, while in others, as the pseudoleukemias, the blood is free of these elements. This fundamental difference has never been explained satisfactorily. It is evident, however, that the primary diseases of the lymphatic-hemapoietic apparatus show definite characteristics not possessed by other tumor groups, but which are explainable by the close embryological relationship of the lymphoblast and myeloblast.

The tumor cells of most of the members of this group are easy of identification, and such neoplasms can be readily classified. There are, however, isolated cases described where the pathological features indicated that the neoplasm was a member of the lymphatic-hemapoietic group, but where the embryological status of the tumor cells could not be definitely determined. These cases must remain, therefore, as unknown quantities in any scheme of classification. The numerous "plasma cell tumors" and the case described by

Norris[51] as a "Multiple Systemic Sarcoma of Myelogenous Origin" are examples of such neoplasms. Until the nature and origin of the tumor cells can be definitely determined a comprehensive classification of the lymphatic-hemapoietic group of diseases will be difficult.

The pathological characteristics of the multiple myelomata, however, put it without question in this group of diseases. In addition, the limited distribution of the tumor growth, which is confined to the skeleton in all save a few instances, and the marked resemblance of the tumor cells to the different bone-marrow elements, suggests that the neoplasm is composed of myeloblasts or derivatives of myeloblasts. Lubarsch[45] plausibly explains the rare cases of extraskeletal myelomata in the liver and lymph nodes by suggesting that such tumors were derived from aberrant myeloid tissue present in those situations.

The different types of multiple myelomata which have been described in the literature have been divided into the following five groups:

1. The myeloblastoma, composed of myeloblasts.
2. The myelocytoma, composed of myelocytes containing neutrophilic granulations.
3. The erythroblastoma, composed of nucleated red cells.
4. The lymphocytoma, composed of cells resembling lymphocytes.
5. The plasmocytoma, composed of cells of "plasma-cell" morphology.

Of the five types the plasmocytoma cannot be regarded as a true myeloma for reasons which we have already discussed. The lymphocytoma is a distinct tumor type, but it cannot be separated from the pseudoleukemias and lymphosarcomas, which involve only the bones, many of which have been described in young individuals. The tumor cells of many of these cases are probably not derived from the myeloblast, and it is very questionable whether they should be classified as true myelomata. The myelocytoma and erythroblastoma are theoretically multiple myelomata, but until more examples of such tumors have been described, they must be included in the classification with reservation. The myeloblastoma is the only one of the five which is unquestionably a well-recognized pathological entity, and in the present state of our knowledge the multiple myelomata term should be reserved for multiple bone-marrow tumors of myeloblastic origin.

BENCE–JONES ALBUMINURIA.

The peculiar body known as Bence-Jones protein was first described by Bence-Jones in 1846 in the urine of a patient of MacIntyre's. He found that a thick yellowish precipitate occurred, when the urine was heated to about 50° C., but that this precipitate dissolved completely on boiling and reappeared when

the solution was cooled. The full significance of this protein in the urine, which had different reactions from those of the ordinary urine albumin, was not recognized at that time, because the case was regarded simply as "mollities ossia rubra."

In 1876 v. Rustizky described his case of multiple bone tumor, to which he gave the name multiple myelomata. The urine examination was apparently normal, and no record was made of the presence or absence of the Bence-Jones protein. It was not until 1889, when Kahler reported a similar case, in which Bence-Jones protein was found in the urine, that any association was drawn between this finding and the disease. Since then many observers, especially the Italians and English, have accepted his conclusion that multiple myelomata and the Bence-Jones protein are inseparable, and Parkes Weber, Moffat and others exclude all cases from the multiple myelomata group which do not show the Bence-Jones protein in the urine. The specific nature of this reacion has, however, been questioned, and a careful review of the literature shows that while true myelomata may not always excrete Bence-Jones protein, the urine of many other conditions may contain this body with all its characteristic reactions.

A review of the latter group, however, brings out the one important fact that in no case in which the urine contained true Bence-Jones protein were the bones or bone marrow definitely proved to be free of pathological processes. Examples of this point were Askanazy's case of lymphatic leukemia, Weinberger's case of chloroma, Fitz's case of myxedema, Seegelken's case of chondrosarcoma, Raschke's case of senile osteomalacia, and the peculiar case described by Gluzinski and Reichenstein. Frank secondary carcinoma of the bones was present in the cases of Bence-Jones proteinuria described by Decastello and Boggs and Guthrie.[130] It is, therefore, obvious that Bence-Jones proteinuria is not strictly a pathognomonic sign of multiple myelomata, though its frequent association with that condition (80 per cent. of the cases according to Rosenbloom) gives it a considerable diagnostic value.

The tests for Bence-Jones protein are quite distinctive and very simple to perform. The urine is heated slowly and an albuminous precipitate forms at a temperature between 50° and 56° C. On further heating the protein dissolves, disappears completely when the solution is boiled, but as the solution cools the precipitate reforms. The same phenomenon of disappearing on boiling and reappearing on cooling is also shown by the precipitate formed by adding potassic ferrocyanide and acetic acid to the urine, and the precipitate formed in the ring contact test of the urine with strong nitric or hydrochloric acid. The urine also gives a violet color with the Biuret test. There are other tests, but the ones mentioned above are the most used and are sufficient to identify the substance.

The urine in case of Bence-Jones proteinuria usually shows on

examination a high acidity, a specific gravity of 1013 and 1020, and a viscidity above the normal. In some cases the reaction was neutral and in one case it was alkaline. In most cases the urine was clear, but in some it was turbid, which Parkes Weber and other English observers claim may be the Bence-Jones protein spontaneously precipitated. In the majority of cases the body was excreted continuously in the urine, though in some no record can be found of this fact. This peculiarity serves to distinguish the true Bence-Jones protein from the albumoses often temporarily excreted in the urine of patients suffering from cachectic or febrile conditions.

The nature of the Bence-Jones protein is not fully understood at present. Some of the earlier writers (Kühne) considered it an albumose, but studies by Moitessier, Magnus-Levy, Abderhalden, and Rostoski and others on the cleavage products obtained from the body by peptic and tryptic digestion, suggest that its composition is more complex than that of an albumose, and more like that of a protein. Abderhalden's theory is that it is a tissue albumin which is manufactured in the organism and takes place in its metabolism, but which is foreign to the blood and is promptly excreted in the urine whenever it enters the blood stream. The experiments of Stokvis, Matthes, and Ellinger have shown that whenever Bence-Jones protein is injected into dogs subcutaneously, intravenously, or per rectum the body is recovered unchanged in the urine. Rostoski was unable to differentiate the Bence-Jones protein from other proteins by the "precipitin reaction." On the whole the researches on its composition have been quite unproductive, and all that we can definitely say is that it is probably an albumin manufactured in the body under pathological conditions, different in composition from any of the other body proteins.

Many theories have been advanced suggesting the origin of the Bence-Jones protein in the body. Magnus-Levy believed that it was an abnormal product of the protein metabolism of the food. Decastello regarded the body as a derivative of diseased kidney epithelium and claimed that it was never found in the urine if the epithelium is normal. Simon, Kühne and Chittenden and Moitessier considered that it was formed by the action of the enzymes of the tumor cells on the proteins in the blood. Parkes Weber looked upon it as a peculiar secretion or degeneration product of the myeloma cells. Rosenbloom endeavored to prove that the body is a cleavage product of osseo-albuminoid, and that its presence, in cases of multiple myelomata, is due to the rapid destruction of bone by the neoplasm. None of these theories have as yet been confirmed.

Many analyses have been made of the organs and body fluids of multiple myelomata cases, and normal cases, with a view to finding out the site of formation of the Bence-Jones protein. Barr, Ribbinck, and Löwe were unable to find the body in the organs of their

cases. Fleischer found a substance giving the reaction of Bence-Jones albumin in the bone marrow of a normal individual. Coriat found a similar body in the pleural fluid of a case of multiple neuritis, though the urine was free from the protein. On the other hand, substances with similar properties to Bence-Jones protein have been obtained by Ellinger, Wood, and Parkes Weber from the bone marrow of multiple myelomata; by Askanazy from the bones of his case of lymphatic leukemia, and by Ellinger from the pleural fluid of his case of multiple myelomata.

It is quite probable that the formation of Bence-Jones protein in the body is connected in some way with the pathological changes in the bones. The frequent association of Bence-Jones proteinuria and multiple myelomata, the involvement of the bones in other cases of Bence-Jones proteinuria, and the occasional demonstration of bodies similar to Bence-Jones protein in the diseased bones, suggest this fact. The mode of formation of this body is still unknown, and so is the method by which it enters the blood and is excreted in the urine. At present our knowledge of Bence-Jones protein is rather theoretical, and many more observations will have to be made before any satisfactory conclusion as to its nature can be reached.

CONCLUSIONS.

1. The multiple myelomata are multiple primary tumors of the bone marrow, occurring, for the most part, in elderly individuals, and manifested during life by deep-seated pain in the bones, characteristic deformities of the skeleton, spontaneous fractures in many bones of the body, severe secondary anemia, and emaciation.

2. The presence of Bence-Jones protein in the urine is characteristic of many cases of multiple myelomata, but it is not a pathognomonic sign of the disease, as it is occasionally found in the urine of other bone conditions.

3. At postmortem, cases of multiple myelomata show the presence of soft, homogeneous tumor masses which replace the cancellous tissue of the bones of the trunk, the vertebræ, ribs, and sternum, and less often of the ends of the long bones of the extremities, the diploë of the skull, and the small bones of the hands and feet.

4. The multiple myelomata are confined to the bones, though a few cases have been reported of extraskeletal growths.

5. The multiple myelomata are composed of cells practically identical with the myeloblasts of the bone marrow or their derivatives. Five different groups of these tumors have been described.

(*a*) Myeloblastoma.
(*b*) Neutrophile myelomata.
(*c*) Erythroblastoma.
(*d*) Lymphocytoma.
(*e*) Plasmocytoma.

The first three tumor types are true multiple myelomata. The lymphocytoma is a distinct tumor type, but as there is considerable doubt regarding the relation of the tumor cell to the myeloblast, it cannot be unquestionably classified as a true myelomata.

The "plasma cell" tumor cannot be considered as a pathological entity until more is known about the origin and mode of development of the plasma cell.

6. The multiple myelomata belong to that group of tumors which are composed of cells derived from the primary mesenchymal "Wanderzellen," and are closely related to the leukemias, chloromas, and other diseases of the lymphatic hemapoietic apparatus.

LITERATURE.

Multiple Myelomata.

* Denotes that references have not been verified.

1. Abrikossoff. Virchows Arch., 1913, 173.
2. Aschoff. München. med. Wchnschr., 1906, 7.
3. Askanazy. Deutsch. Arch. f. klin. Med., 1900, 68.
4. Bechtold.* Inaug. Diss., Wurzburg, 1902.
5. Bell and Keenan.* Montreal Med. Jour., 1902, 81.
6. Benda. Berl. klin. Wchnschr., 1908.
7. Bender. Deutsch. Zeitschr. f. Chir., 1902, 65.
8. Berblinger. Frankfürter Zeitschr. f. Path., 1910, 1911, 6.
9. Borst. Die Lehre von den Geschwulsten, 1902, i, p. 492.
10. Bradshaw. Med. Chir. Tr., 1898, 1899, 81 and 82.
11. Buchstab and Schaposchnikow.* Russ. Arch. de Path. de Méd. Clin. et de Bact., 1899, 7. Ref. Central f. allg. Path., 1899, 10.
12. Buch.* Inaug. Diss., Halle, 1873.
13. Charles and Sanguinetti. Brit. Med. Jour., 1907, i, 196.
14. Christian. Jour. Exp. Med., 1907, vol. ix.
15. Dalrymple. Dublin Quart. Jour., 1846, ii, p. 85.
16. Dóvé.* La Normandie Médicale, 1907, 22. Rev. Médicale de Normandie, 1907, 8.
17. Devic and Beriel. Rev. de Chir., 1906, ii, 459.
18. Dick. Tr. Chicago Path. Soc., 1903, vi, 6.
19. Ellinger. Deut. Arch. f. klin. Med., 1899, 62.
20. Ewald. Wiener klin. Wchnschr., 1897, 10.
21. Finkelstein.* Diss., Strassburg, 1900.
22. Fischer. Berl. klin. Wchnschr., 1912, 50.
23. Gluzinski and Reichenstein. Wien. klin. Wchnschr., 1906, 19.
24. Gravitz. Virchows Arch., 1879, 76.
25. Grosch.* Dissertation. Munich, 1906.
26. Groves.* Ann. Surg., 1913, p. 163–170.
27. Hammer. Virchows Arch., 1894, 137.
28. Harbitz.* Norsk. Mag. f. Laegevidens Kaben, 1903, 54.
29. Hart. Frankfürter Zeit. f. Path., 1909, 3.
30. Herrick and Hektoen. Medical News, 1894, 65.
31. Herz. Wien. med. Wchnschr., 1908, 53.
32. Herz. Folia Hemat., 1912, xiii, 1.
33. Hirschfeld. Folia Hemat., 1909–1910.
34. Hoffman. Ziegler's Beitr. zur path. Anat., 1904, 39.
35. Heuter. München. med. Wchnschr., 1907, 54.
36. Israel. Deutsch. med. Wchnschr., 1890.
37. Jellinek. Virchows Arch., 1904, 177.
38. Jochmann and Schumm. Zeit. f. klin. Med., 1902, 46.
39. Jores. Deutsch. med. Wchnschr., 1906, 21.
40. Kahler. Wiener med. Presse, 1889.
41. Kalischer. Deutsch. med. Wchnschr., 1901, 4.

42. Kaufmann. Lehrb. Spez. Path. Anatomie, 1911.
43. King. Jour. Am. Med. Assn., April 15, 1911.
44. Lazarus.* Diss., Berlin, 1890.
45. Lubarsch. Virchows Arch., 1906, 184.
46. MacCallum. Jour. Exp. Med., 1901, 1905, 6.
47. MacIntyre. Med. Chir. Tr., 1850, 33.
48. Marchand. Berl. klin. Wchnschr., 1886, 23.
49. Marckwald. Virchows Arch., 1895, 141.
50. Menne. Virchows Arch., 1906, 183.
51. Norris. Proc. New York Path. Soc., new series, November, 1906, vol. vi.
52. Norris and Vance. Proc. New York Path. Soc., 1912, vol. xii, Nos. 7 and 8.
53. Nothnagel.* Festschrift, R. Virchow, 1891, ii, p. 155.
54. Paltauf. Lubarsch u. Ostertag Erg. d. allg. Path., 1896, iii, p. 652.
55. Pappenheim. Folia Hemat. Suppl., 1907, iv, 1909, vii.
56. Permin. Virchows Arch., 1907, 189.
57. Pertik. Wiener med. Wchnschr., 1890.
58. Quackenboss and Verhoeff. Jour. Med. Research, 1906, 10.
59. Ribbert. Central f. allg. Path., 1904, xv.
60. Runeberg. Arch. f. klin. Med., 1883, 33.
61. v. Rustizky. Deutsch. Zeit. f. Chir., 1873, 3.
62. Saltykow. Virchows Arch., 1903, 173.
63. Scheele and Herxheimer. Zeit. f. klin. Med., 1904, 54.
64. Schoenenberger. Virchows Arch., 1901, 165.
65. Schmorl. München med. Wchnschr., December, 1912, vol. lii.
66. Schmidt. Lubarsch. u. Ostertag's Erg., 1897, iv, 531.
67. Schutz. Deutsch. Arch. f. klin. Med., 1914, 113, B, 5064.
68. Seegelken. Deutsch. Arch. f. klin. Med., 1897, 58.
69. Senator. Berl. klin. Wchnschr., 1899.
70. Shennan. Edinburgh Med. Jour., April and May, 1913.
71. Simmonds. München. med. Wchnschr., 1906 and 1911.
72. Sorge.* Diss., Jena, 1900.
73. Spiegelberg.* Diss., Frankfurt, 1894.
74. Sternberg, C. Lubarsch u. Ostertag's Erg., 1903 (9) (2), p. 449.
75. Sternberg, C. Verhand. der deutsch. Path. Gesell., 1903, p. 34.
76. Sternberg, C. Zeitschr. f. Heilk., 1904.
77. Sternberg, M. Nothnagel's spec. Path. u. Ther., 1899, 7, Abth. 2.
78. Stuma.* Surg. Gyn. and Obst., xv, Nr. 6, p. 653.
79. Suszman.* Diss., Berlin, 1897.
80. Thomas. Boston Med. and Surg. Jour., 1901, 145.
81. Tschistovitsch and Kolessnikoff. Virchows Arch., 1909, 197.
82. Verco. Austral. Med. Gaz., 1903, xxii.
83. v. Verebely. Beit. f. klin. Chir., 1906, 48.
84. Virchow. Die Frank Geschwulste, 1864, ii, p. 57.
85. Vignard and Gallavardin. Rev. de Chir., 1903, 27.
86. Voit and Salvendi. Zeitschr. f. klin. Med., 1904, 54.
87. Warstat. Ziegler's Beitrage, January 18, 1913.
88. Weber, H. Tr. Path. Soc., London, 1867, 18.
89. Weber, F. Parkes. Am. Jour. Med. Sc., 1903, 126.
90. Weber, F. Parkes. Med. Chir. Tr., 1903, vol. lxxxvi.
91. Weber, F. Parkes, and Ledingham. Proc. Royal Soc. Med., Path. Soc., 1909, 2. Folia Hematol., 1909, viii, 14.
92. Wieland. Virchows Arch., 1901, 166.
93. Williams, Evans and Glynn. Lancet, November 12, 1910.
94. Wieland. Diss., Basel, 1893.
95. Winkler. Virchows Arch., 1900, 161.
96. Wright. Johns Hopkins Hospital Reports, 1900, ix.
97. Zahn. Deutsch. Zeitsch. f. Chir., 1885, 22.
98. Zinninger. Amer. Med., 1904, 7.

Additional References.

Kahn. Med. Record, New York, 1914, lxxxv, 843–848.
Mieremet. Virchows Arch., 219, Heft i.
99. Ghon and Roman. Folia Hematologica, 1913 (literature on the "Plasma Cell" question).

For Literature on the Bence-Jones Protein, see:

100. Boggs and Guthrie. Johns Hopkins Hosp. Bull., 1912, 1913.
101. Moffat. Lancet, 1905.
102. Rosenbloom. Biochem. Bull., December, 1911, vol. i, No. 2.

For Literature on Bone Marrow Formation, see:

103. Butterfield. Deutsch. Arch. f. klin. Med., 1908, 92.
104. Maximow. Arch. f. Micros. Anat., 1911, 76.

MASSIVE HEMORRHAGES FROM THE STOMACH WITHOUT DEMONSTRABLE ULCER.

By Alexis V. Moschcowitz, M.D.,

Professor of Clinical Surgery, College of Physicians and Surgeons, Columbia University; Attending Surgeon, Mount Sinai Hospital; Visiting Surgeon, Har Moriah Hospital, New York.

Early in 1915, within a period of less than one month, I had the opportunity to operate upon four patients, upon whom the unequivocal diagnosis of a bleeding ulcer of the stomach had been made, both by myself and by several very competent colleagues; and yet none of the operations failed to reveal even the slightest tangible lesion of the stomach. In spite of a most unfavorable outlook in all of these cases, and practically a hopeless one in two, all of these patients recovered. The fortunate outcome, while gratifying, leaves me, nevertheless, with a sense of incompleteness of the study of the pathological data, inasmuch as my observations are based only on the examination of the unopened stomach *in vivo* and not on postmortem material. Clinically, nevertheless, these cases are of profound interest, and even with the shortcomings I have mentioned, deserve the fullest report. The histories of these cases are the following:

Case I.—Chas. R. Austrian, aged thirty-six years, was admitted to the Medical Division of Mount Sinai Hospital, upon the service of Dr. Manges, January 7, 1915. His illness was of two and a half years' duration, and began with the vomiting of a large quantity of blood without any premonitory symptoms. This hematemesis continued for a few days and then ceased for three or four months, when he again vomited large amounts of blood during several consecutive days. This cycle was repeated on two further occasions. After the fourth attack the patient entered a hospital in Brooklyn, where he was operated upon. An incision through the upper part of the right rectus was made, but apparently nothing was found to account for the hematemesis; the appendix was removed. The condition of periodic profuse hematemesis was unchanged by the operation. Altogether there had been nine such attacks within two and a half

years, each attack lasting several days, so that by the termination of the last attack the patient was profoundly anemic, and anxious to obtain relief, if possible, even by further operation.

The physical examination revealed a systolic murmur over the whole precordium, with accentuation of the second sound. The abdomen showed a peculiar fulness of the epigastrium, with marked local tenderness to the right of the median line; the liver was palpable one and a half fingers below the free border of the ribs. The patient, just having recovered from an attack of hematemesis, was greatly prostrated, emaciated, and apparently very anemic. At no time during his observation at the hospital was blood found in the stomach contents or in the feces. Test meals on several occasions showed, on an average, a total acidity of 85 to 90, and free HCl 50 to 60. Hemoglobin, 63 per cent. Two roentgen ray examinations were suggestive of adhesions around the pylorus, with dilatation and ptosis of the stomach.

I was requested to see the patient by Dr. Manges; we agreed that the patient, in all probability, suffered from an ulcer at the pylorus, with a somewhat atypical symptom-complex, and advised operation.

Operation, January 30, 1915. Five-inch median epigastric incision. The liver was found to be enlarged, as was indicated in the physical examination. It was of a deep purplish color, and soft in consistency; its capsule was wrinkled, not tense. In the region of the cicatrix of the previous operation there were present massive adhesions, which united the omentum, the liver, and the abdominal parietes. These were carefully freed, in order to permit a thorough exploration of the stomach, pylorus, and duodenum. Even the most painstaking examination failed to reveal the slightest suspicion of an ulcer; the only abnormality was a somewhat greater tortuosity of the gastric vessels than is normal. A specimen was removed from the liver for pathological study, and was reported by Dr. F. S. Mandlebaum as "congestion." The postoperative course was marred by pneumonia, but the patient was discharged with a well-healed scar February 13.

I saw and examined the patient October 3, 1915. In the interval there had been no further attack of hematemesis; in fact, the patient vomited only once or twice during that time. The patient is, however, quite dyspneic, and is beginning to suffer more and more from his cardiac trouble.

Epicrisis. Quite properly it might be argued that the primary cause of the hematemesis in this case is to be looked for in the cardiac condition; this caused secondarily the hepatic congestion, which in turn was followed by the gastric hemorrhages. Granted that such is the case, we must, nevertheless, assume a loss of continuity in the gastric mucosa and a subjacent vessel to permit the escape of such large amounts of blood. The only other hypothesis possible is that of hemorrhage per diapedesim, a theory long since disproved. I

believe that an ulcer was present, but that it was so small as to escape detection. It is on this account that I include this case in my report.

CASE II.—Morris I., Russian, aged thirty-three years, was admitted to my service at Mount Sinai Hospital February 18, 1915. For the past four years the patient had been suffering from pain in the epigastrium, which radiated to the back at about the level of the tenth dorsal vertebra; the pain was relieved by the ingestion of food for a period of one to two hours. Associated with this pain there occurred also vomiting, which ensued about one hour after eating. Very frequently the patient also vomited large amounts of pure blood, followed by tarry stools. The patient felt very weak, and lately had lost seventeen pounds in weight.

The physical examination was entirely negative except for tenderness at McBurney's point and a localized area of exquisite tenderness in the epigastrium to the right of the median line. The report of the roentgen-ray examination made by Dr. Jaches was "duodenal ulcer."

Operation, February 20. A short Sprengel incision through the left rectus was first made, but in order to permit a more thorough examination the incision was extended so as to divide both recti. The stomach was found to be somewhat dilated, but with this exception absolutely nothing of an abnormal nature was found; neither in the stomach, duodenum, gall-bladder, liver, nor pancreas. The appendix was removed and was found to be normal.

After an uneventful convalescence the patient was discharged, with a well-healed scar, March 9.

The next case is perhaps the most interesting of my series:

CASE III.—Minnie R., Canadian, graduate nurse, aged twenty-five years, was admitted to the hospital February 14, 1915.

Past History. Typhoid fever nine years ago; about three years ago, while in training school and on night duty, she complained for a few days of a gnawing feeling in the epigastrium after the midnight meal. Test meals taken at that time were negative. Patient was considered a neurasthenic, and never was ill enough to be taken off duty.

February 14, 1915, at 2 P.M., she vomited about thirty ounces of blood, without any premonitory symptoms; at 4 P.M., a like amount of blood was vomited; at 9 P.M., fifty ounces of blood were vomited, and the patient fainted. She was transferred to the hospital and was treated with morphin, rest in bed, and ice-bag to the epigastrium. February 15 the hemoglobin percentage was 47. In the evening the patient again vomited thirty ounces of blood and again fainted. During the next three days there was a cessation of vomiting, but there was continuously melena, and in consequence the hemoglobin percentage dropped lower and lower. Operative interference was considered, but was thought inadvisable on account of the poor condition of the patient.

On February 19 the patient was transfused by the citrate method by Dr. Lewisohn, raising the hemoglobin percentage from 35 to 55 per cent. In spite of this transfusion the condition of the patient became continuously worse. She was so anemic that no accurate measurements of the hemoglobin percentage were obtainable with the Sahli instrument. I therefore decided upon operation.

At midnight of February 20, after a preliminary transfusion by the citrate method by Dr. Lewisohn, 800 c.c. being transfused, the stomach was exposed through a median epigastric incision. All the viscera in the upper part of the abdomen were thoroughly explored, particular attention being paid to the stomach and duodenum. After carefully exploring the anterior wall of the stomach and finding nothing suspicious, the lesser peritoneal sac was entered through the gastrohepatic omentum and the entire posterior wall examined with the greatest care. Absolutely nothing of an abnormal nature was found. In sheer despair I made a posterior retrocolic gastro-enterostomy and excluded the pylorus.

On the following day her condition was excellent. There was still some melena, but this could very readily be accounted for by bleeding which had occurred prior to the operation.

Condition of the patient was perfectly satisfactory on my morning visit to the hospital on February 22. At twelve o'clock noon of that day I was hurriedly summoned to the hospital by a message that the patient had suddenly gone into collapse, and was in a moribund condition. An acute dilatation of the stomach was considered to be possible, and I therefore passed a stomach-tube and withdrew over a quart of bright red blood; this was followed by a lavage of the stomach with ice-water until the washings returned clear.

From that time on the condition of the patient began to improve; the hemoglobin slowly increased, and she was discharged well four weeks later.

Epicrisis. The history and course of this case is typical of the "exulceratio simplex of Dieulafoy." The sudden profuse hematemesis without any preceding gastric symptoms is particularly suggestive. The postoperative course is also most interesting. The occurrence of an almost fatal hemorrhage thirty-six hours after operation is very interesting, and will no doubt be regarded by many as proof of the failure of operation. To my mind, however, such an argument is entirely erroneous; at best it may be argued that I selected in this case an indirect method to stop the hemorrhage instead of a direct method. Had the condition of the patient been better I would have incised the stomach and searched for the bleeding-point, with certainly a greater promise of success.

CASE IV.—Esther K., had been under hospital observation for more than a year. When admitted the first time to the pediatric service of Dr. Koplik, April 24, 1914, she was two years and three months old. Measles and pneumonia one year ago. Furthermore,

it is important to note in the history that five months ago the patient was operated upon at another institution for a congenital dislocation of the hip by the bloodless reduction method, and that the duration of the anesthesia was two hours. On the day following this anesthesia the patient vomited blood for the first time. The symptom recurred four times within the next two days, and then apparently ceased. Four weeks prior to her admission to Mount Sinai Hospital there was another cycle of hematemesis, and again one day before admission. The last amount was 175 c.c. The child has had fever for two days, with profuse sweating; there was present also edema of neck, face, and feet. The last attack of hematemesis was followed by tarry stools.

The physical examination upon admission revealed the following facts worthy of record: (1) a profound anemia; (2) a short systolic murmur at the apex, not transmitted; (3) a congenital dislocation of the left hip.

April 25, 9 c.c. of rabbit serum were injected into the buttock. This was followed in twenty minutes by a universal urticaria and itching, but no cyanosis and no dyspnea; the urticaria disappeared in ten minutes. Patient was profoundly toxic and in a stuporous condition; the pulse became imperceptible and required energetic stimulation.

April 26—Hemoglobin (Sahli)	12	per cent.
Red blood cells	1,689,000	
Leukocytes	10,000	
Polynuclears	62	per cent.
Mononuclears	38	"

A loud murmur, probably hemic in character, was heard at the base. The vomiting of blood continued.

April 29 patient was transfused by Dr. A. Hyman, by the cannula method, raising the hemoglobin from 12 per cent. to 48 per cent. After the transfusion the child appeared to be in excellent condition, was perfectly conscious, and took nourishment well.

The vomiting of blood ceased, and in spite of tarry stools the hemoglobin rose steadily and reached 62 per cent. on May 12. Without any visible bleeding, either from mouth or rectum, there occurred a recession in the percentage of the hemoglobin, so that by June 1 it was only 40 per cent. The general condition of the patient, however, was much improved, and the child was discharged June 20, 1914, at the request of the mother.

Patient was readmitted June 25, 1914, or five days later. Since her discharge from the hospital the condition had rapidly deteriorated; the anemia rapidly became worse, and the face and neck were becoming more puffy. The mother stated that the child had had several tarry stools. On the day preceding the readmission to the hospital the child vomited blood, and there was also melena. June 26 the hemoglobin percentage was only 22, with a red blood cell

count of 2,150,000. For a long time thereafter citrate of iron was administered hypodermically. Several attempts were made to obtain a satisfactory test meal, but they were not successful until July 17, when 10 c.c. of partly digested, non-odorous stomach contents were obtained, which did not show blood, either chemically or microscopically; total acidity 50, no free HCl. Thereafter blood was found in the stools continuously until July 29. Under the citrate of iron treatment the hemoglobin rose steadily and reached practically the normal by August 12, 1914, when the child was again discharged in an excellent condition.

The patient was readmitted February 15, 1915. Since her previous discharge the condition had remained good up to seven weeks before admission, when the mother noticed an increasing pallor, ascribed to the presence of tarry stools; but there was no vomiting. On the day preceding admission, at 9 P.M., the last previous meal having been taken at 2 P.M., she vomited a glassful of dark coagulated blood, and again at 11 P.M. half a glassful of bright red blood.

The physical examination revealed, in addition to the previous findings and the anemia a spleen, which reached 1.5 cm. below the free border of the ribs. On the day of admission the vomiting of blood continued, and there were also several tarry stools. Examination of the blood showed the following:

Hemoglobin	28	per cent.
Red blood cells	1,600,000	
Leukocytes	20,000	
Polynuclears	89	per cent.
Small lymphocytes	10	"
Large lymphocytes	1	"
Moderate poikilocytosis		

On this day the child was transfused by Dr. Lewisohn by the citrate method. Ten hours after transfusion the hemoglobin was 33 per cent.

February 16th, profuse hematemesis.
February 17th, and 18th, several tarry stools.

Hemoglobin	30	per cent.
Red blood cells	800,000	
Leukocytes	26,000	
Polynuclears	90	per cent.
Large lymphocytes	10	"
February 20th. Hemoglobin	25	"

February 21. I was requested to see the patient, and advised an exploratory operation, the most probable diagnosis being that of an ulcer in the vicinity of the pylorus; the operation to be preceded by another transfusion, in order to raise the hemoglobin to safe limits.

February 22. Hemoglobin only 14 per cent.; 450 c.c. of blood were transfused by Dr. Lewisohn, which raised the hemoglobin to

37 per cent. Immediate operation. Median epigastric incision four inches long. Considerable serous fluid in the free peritoneal cavity. A very thorough examination of the stomach and duodenum failed to reveal even a suspicion of an ulceration. The liver appeared to be normal. The spleen was slightly enlarged.

After operation there was absolutely no change in the condition of the patient, as may be seen by the following notes:

February 23. Hemoglobin, 50 per cent.; bleeding time, nine minutes.

February 26. Hemoglobin, 45 per cent.; bleeding time, eight minutes.

February 28. Hemoglobin, 28 per cent.; coagulation time, six minutes; bleeding time, eight minutes.

March 2. Hemoglobin, 25 per cent.; coagulation time, six minutes; bleeding time nine minutes.

March 3. Hemoglobin 17 per cent.; coagulation time, five minutes; bleeding time, eight minutes. On this day the patient was seen by Dr. Koplik, who, in view of the futility of all therapy, and because of the continuation of the bleeding, advised another transfusion. This was done on March 4 by the Unger method, raising the hemoglobin to 50 per cent.

March 5. Hemoglobin, 46 per cent.; coagulation time, seven minutes; bleeding time, fourteen minutes.

March 6. Hemoglobin, 50 per cent.; coagulation time, five minutes; bleeding time, nine minutes.

March 7. Hemoglobin, 43 per cent.

March 8. Hemoglobin, 38 per cent.

Thereafter the hemoglobin in spite of occasional tarry stools remained stationary. The wound being perfectly healed, the child was retransferred to the service of Dr. Koplik; and I wish to acknowledge my indebtedness to him for both the pre-operative and final notes of the case.

April 2. Patient vomited four ounces of clotted and fluid blood. Melena.

April 3. Melena.

April 5. Hemoglobin, 16 per cent.

April 13. Patient vomited about eight ounces of clotted and fluid blood. On this day examination of the blood revealed the following values:

Hemoglobin	15 per cent.
Red blood cells	1,616,000
Leukocytes	8,800
Polynuclears	44 "
Small lymphocytes	36 "
Large lymphocytes	10 "
Transitionals	1 "
Myelocytes	5 "
Basophiles	1 "
Myeloblasts	2 "
Normoblasts	4 per 100 leukocytes
Megaloblasts	1 " "

Marked pallor of the red cells; moderate poikilocytosis and anisocytosis; polychromatophylia.

April 15. A transfusion by Dr. Lewisohn of 380 c.c. of citrated blood raised the hemoglobin from 13 to 30 per cent.

After this final transfusion for some unexplained reason the vomiting and melena ceased; the hemoglobin began to rise; patient was soon able to leave the bed, and was finally discharged in very good condition May 3, 1915.

These are the histories of the four personally observed cases; all of them seen within a period of less than one month and three within a period of two days. I confess to considerable chagrin and disappointment, as in all of them I had made, or at least concurred in, the diagnosis of a bleeding ulcer of the stomach or duodenum with a degree of confidence which bordered upon positiveness.

REVIEW OF THE LITERATURE. In the older medical literature the statement is frequently made that bleeding from the stomach may occur by diapedesis; but with the advent of careful pathological and microscopic examinations the theory of bleeding by diapedesis has been found to be untenable. The generally accepted view now is that all bleeding from the stomach, particularly that of larger quantities, must be the result of a defect in the mucosa. Such a defect was, however, not determinable by the conventional methods of examining the stomach *in vivo*, for I assume that it would have been unjustifiable on my part, in view of the poor condition of my patients, to make a wide opening into the stomach, to permit of thorough interior exploration.

A study of my personally observed gastric material and a critical review of the literature upon the subject lead me to the conclusion that all defects of the gastric mucosa other than neoplastic may be grouped under the following three forms:

1. The "*mucous erosions*,"[1] so called, accredited to Einhorn.
2. The "*exulceratio simplex*,"[1] so called, accredited to Dieulafoy.
3. The "*true gastric ulcer*,"[1] of Cruveilhier.

1. "*Mucous Erosions.*" I have had very little experience with this group, certainly not sufficient to warrant me to pass an opinion upon the subject, but a study of Einhorn's publications,[2 3 4 5] as well as of similar articles by Pariser,[6] Mintz,[7] Hageman and Jones,[8 9 10]

[1] It is regrettable that these terms are used so indiscriminately and interchangeably by different authors. I believe that the nomenclature, as I use it, is correct.

[2] Berl. klin. Wchnschr., 1895, p. 435.

[3] Jour. Am. Med. Assn., 1870, p. 1079.

[4] New York Med. Jour., 1908, p. 777.

[5] Diseases of the Stomach, New York, William Wood & Co.

[6] Pariser, Berl. klin. Wchnschr., 1900, p. 954.

[7] Ztschr. f. klin. Med., 1902, p. 115.

[8] Inaug. Dissert., Freiburg, 1909.

[9] Jour. Am. Med. Assn., October 14, 1911, p. 1265.

[10] Northwest Med., February, 1912.

will very quickly show that none of my cases could very well belong to this group.

The symptomatology and physical signs of this malady (if at all a clinical entity, which is doubted by some observers) are not at all well marked; the chief characteristics of the ailment are the presence of small bits of mucous membrane in the lavage water and the absence of hematemesis. The presence of very profuse gastric hemorrhages in all of my cases is sufficient to exclude them from this group.

2. "*True Gastric Ulcers.*" I have also excluded my cases from the third group, or the group of true ulcers. This exclusion must, of course, be accepted with a certain amount of mental reservation. I justify my procedure upon a fairly extensive operative experience with ulcers of the stomach and duodenum, which has led me to the belief that their recognition is a comparatively easy matter. It should also be taken into consideration that my professional pride would naturally have acted as an incentive to the most painstaking examination in these four important cases, in order that the preoperative diagnosis of ulcer might be upheld. I must assume, therefore, that the gross ulceration, or true gastric ulcer, I so confidently expected to find, did not exist.

3. There remains therefore only group two, or "*exulceratio simplex*" of Dieulafoy, so called. I am confident that if my cases are studied from the point of view of diagnosis it will be found to correspond to all the requirements attributed to this group.

While Dieulafoy has been antedated by a number of writers, notably Chiari[11] and Murchison,[12] in the report of cases of massive or even fatal gastric hemorrhages, in which the autopsy revealed either a trivial lesion or even an entire absence of any lesion, it was undoubtedly his masterly and vivid description, and more particularly the recovery of his second case, after an operation, deliberately undertaken to check the hemorrhage, which has awakened the interest of the medical profession to the malady under discussion; in fact, we frequently find it spoken of as "Dieulafoy's ulceration." For the sake of historical correctness I may be pardoned for abstracting briefly Dieulafoy's two cases.

Dieulafoy[13] reports the following cases:

Case I.—Male, aged twenty-seven years, admitted to the hospital November 13, 1896, for hematemesis, which began without any premonitory symptoms at noon of the day of admission. Patient states that he lost two or three liters of blood; although Dieulafoy doubts the correctness of this statement, he is certain that the loss of blood must have been very great. He was treated by absolute rest, ice-bag to the abdomen, and ergotin injections. The hema-

[11] Prag. med. Wchnschr., 1882, p. 489.
[12] Tr. Path. Soc., London, 1870, xxi, 162.
[13] Bull. de l'Acad. de méd., Paris, 1898, p. 49.

temesis recurred that night, and was followed by melena. The total amount of blood lost was estimated at four liters. Patient was in a desperate condition. Dieulafoy considered the advisability of surgical interference, but abandoned it. An intravenous saline infusion was followed by temporary improvement only, as patient died within less than thirty hours from the onset of the gastric hemorrhage.

The autopsy revealed the following points of interest. On incising the stomach half a liter of blood was found, but to everybody's surprise, at first, no ulcer was seen. Carefully washing away the blood, there was discovered 2 cm. distal to the cardia, a very superficial "exulceration" of the size of a five franc piece. The borders of this exulceration were not indurated, nor elevated; upon the base, which was grayish white and soft, there were to be seen two or three small ecchymotic spots, and two craterlike erosions. In one of these there was seen a small open arteriole, into which it was possible to introduce the point of a pin.

The subsequent histological examination showed that the defect in the stomach involved only the mucosa and submucosa; and even the latter not throughout the entire defect. All the other coats were normal. In the bottom of one of these crater-like erosions there was an open arteriole, which was the source of the fatal hemorrhage. The coats of this arteriole, a branch of the coronary artery of the stomach, showed neither a periarteritis nor an endarteritis. The veins in the vicinity were dilated and thrombosed, and explained the ecchymotic appearance above mentioned.

When Diuelafoy saw the specimen he regretted extremely his decision not to call for surgical aid, and fully made up his mind to act differently on a future occasion. This occasion presented itself in

Case II.—On October 18, 1897, there was admitted to his hospital service a male, aged twenty-two years, who gave the following history. On the evening of October 7, after having eaten a hearty meal, he became nauseated and vomited a quantity of blood, which he estimated at one or two liters. He was very much weakened thereby, but passed a comfortable night. On the following day he again vomited large amounts of both fluid and clotted blood. Prior to this attack patient never had any gastric symptoms.

When admitted to the hospital he presented all the symptoms of a profound anemia. From his appearance, Dieulafoy estimated that he must have lost three or four liters of blood.

From the history and symptoms, and by a process of exclusion, Dieulafoy arrived at the conclusion that this patient was suffering from the same kind of "exulceration" as Case I. While he knew from his previous experience that if something energetic were not undertaken he would probably lose the patient, Dieulafoy hesitated to advise so radical a procedure, in the state of gastric surgery, as it existed at the time; he therefore temporized and treated the patient expectantly.

On October 16 patient vomited exactly 1 liter of fluid and clotted blood. Extreme pallor, pulse imperceptible. Being certain that the patient would die upon the accessoin of another hemorrhage, he referred the patient to a surgeon, M. Cazin.

Cazin operated only upon the insistence of Dieulafoy, as the outlook otherwise was hopeless. On exposing the stomach nothing suspicious was found, neither to sight nor to touch. The stomach was therefore incised and the interior everted and explored. At first nothing was found, but on cleaning away the stomach contents he was rewarded by seeing a tiny "exulceration" on the posterior wall of the stomach near the cardia, about the size of a 50-centime piece. On gentle sponging, bleeding began again; however, it was not an ordinary gastric ulcer, with indurated and elevated borders, but merely an exulcerated surface, comparable to that described in Case I.

The ulcer was sutured from within the stomach, and the operation finished in the uusal manner. Patient recovered.

In addition to these two personally observed cases Dieulafoy was able to find three other similar cases in the practice of his colleagues (Michaux, Gilbert (2)); also one case which is published by Luys[14] and by Lepine and Bret.[15]

Dieulafoy's observations apparently did not fall on very fertile ground except in England, because it is in England only that we find similar cases reported with any degree of frequency. Cases of a similar nature, however, to the number of less than fifty have been reported in England by Steven, Mackenzie, Hood, Armstrong (Montreal), Mansell Moullin, Hale White, Dawson, Harrington, Mayo Robson, Symonds, Moynihan, Eve, Guilford and others. Very few cases have been reported on the Continent, Banti, Monprofit, Harttung, Hampeln, Berger, etc. It is somewhat difficult to estimate the frequency of the malady in the United States, judging merely from the literature; this is due to the fact that almost all authors, writing upon this or allied subjects, speak of these exulcerations with such a degree of familiarity as to lead one to believe that they are matters of frequent personal experience; and yet when we come to look for actual and bona fide observations we find but very few. An exception is Deaver,[16] who in a paper entitled "Gastric Hemorrhages," distinctly states that he has operated in six cases belonging to this group. It is to be regretted, however, that none of these cases are reported in detail. It is very probable that some of the cases mentioned by W. Gilman Thompson[17] belong to this group; and it is also possible that one or another of the ten cases of operation for gastric hemorrhage reported by Lund, Joslin and

[14] Bull. de la Soc. anat., 1896, p. 660.
[15] Arch. de Méd. expér. et d'anat. path., 1893, p. 254.
[16] Surg., Gynec. and Obst., xviii, 294.
[17] Am. Jour. Med. Sc., September, 1905, p. 357.

Murphy[18] may be of a similar nature, because in some of these a fairly adequate search during the operation failed to reveal any bleeding point or ulcer. Cases have also been reported by Abbe,[19] Andrews and Eisendrath,[20] Rodman[21] and others.

I have permitted myself considerable latitude in admitting cases into this group, but there are some, reported under this heading, which, for various reasons, I have found necessary to exclude. I mention, for instance, the cases reported by Jones,[22] in which at autopsy the stomach and upper bowel were found to be free from ulcer, erosions, scars, eroded vessels; in fact, everything that might have led to hemorrhages. Jones claims that the bleeding had taken place from a gastric erosion and that sufficient time had elapsed for healing to take place.

I shall also exclude the case observed by Pilliet and Deny.[23] Fatal hematemesis in an insane male person, aged fifty-eight years. At autopsy a number of minute "hemorrhagic erosions" were found, both in the stomach and duodenum. My reasons for excluding this case are that there was a history of the swallowing of a number of metallic foreign bodies which obviously may have produced the lesion.

An exceedingly accurately observed case is that of Hirsch.[24] I am, however, of the opinion that it does not properly belong into this group, because a scar was found in the stomach, from the center of which the hemorrhage issued; and I believe that Dieulafoy's ulcerations are particularly characterized by the absence of scars. The patient was a female, aged nineteen years. There was a history of chlorosis and also of gastric disturbances with hematemesis. After a railway accident, however, without any direct trauma to the abdomen, there was a very profuse gastric hemorrhage. Autopsy at first showed nothing; only after repeated careful examinations there was discovered a white scar the size of a lentil, having in its center a pin-head sized perforation leading into an open vessel.

Symptomatology and Physical Signs. A typical example of "exulceratio simplex" Dieulafoy can be said to have only one well-marked symptom, namely, profuse hematemesis. This is such a characteristic symptom that we may divide the entire symptomatology into two parts, (1) before, and (2) after the occurrence of the hematemesis.

Before the occurrence of the hemorrhage the history and physical signs are to all intents and purposes negligible. We find in a majority of instances that the afflicted individuals have no complaints refer-

[18] Boston Med. and Surg. Jour., August 4, 1904.
[19] New York Med. Jour., May, 1891.
[20] Ann. Surg., 1899, xxx, 393.
[21] Philadelphia Med. Jour., June 9, 1900, p. 1302.
[22] Northwest Med., February, 1912.
[23] Gaz. méd. de Paris, 1893, p. 401.
[24] Berl. klin. Wchnschr., 1896, p. 847.

able to the stomach. The appetite and digestion are fair, and the general health is so good that there does not exist at any time suspicion of impending danger. Suddenly and without any warning the patient vomits blood. It is rather characteristic that the first vomiting is so profuse that the patient shows systemic signs of bleeding. There are cases recorded in which even the first hemorrhage was fatal.

The physical signs before hemorrhage are not known, for obvious reasons; but in view of the absence of symptoms before hemorrhage it is safe to assume that the physical signs must also be negative.

After hemorrhage has taken place the symptoms and physical signs which govern the disease are merely those of a profound anemia. Examination of the stomach reveals nothing noteworthy. In the few cases in which the gastric contents were examined, nothing characteristic has been found. In some cases a marked hyperacidity, in some normal values, and in others even a hypoacidity has been found.

The disease affects most frequently females in the early twenties; but males in the later years of life, and even children, are not immune.

Hale White,[25] under the title of gastrostaxis, also called attention to gastric hemorrhages, which are not caused by true ulcers, and in many of which the true source of the bleeding has remained undiscovered. If his case reports are carefully examined it is manifest, that he has been describing nothing more nor less than Dieulafoy's ulcer. In a few of the case-reports the source of the bleeding was not discovered, but this was probably due to hasty, or at least insufficient examination.

Pathologically these cases differ from the gastric erosions of Einhorn, in the fact that while in the latter the defect in the gastric mucosa is so superficial as not to involve even the entire thickness of the mucosa (indeed, no postmortem examinations have ever been made, to my knowledge), the defect in Dieulafoy's ulcerations extends at one point, at least, throughout the entire thickness of the mucosa, involves the submucosa, and has eroded a vessel of appreciable size. It is in this characteristic only that we can account for the presence of notable hemorrhages in the latter and their absence in the former. Neither one of these ulcerations is accompanied by any palpable induration, infiltration, or thickening. When eventually such a lesion heals it does so without any recognizable cicatrix formation, and therefore never causes any deformities in the shape of the stomach. Finally, in true ulceration of the stomach, the defect invades more of the coats of the stomach, even to and through the serosa. There is considerable infiltration of massive induration, which renders their recognition by the examining finger very easy,

[25] Lancet, November 3, 1906.

and when such ulcerations heal they do so by the formation of a true cicatrix, resulting in appreciable deformity of the stomach.

The question of the relationship between the simple exulceration of Dieulafoy and the true gastric ulcer of Cruveilhier has not yet been definitely decided. Some observers take a definite affirmative stand, notably Gerhard;[26] others, as, for instance, Langerhans,[27] deny any relationship between the two, or admit it only as a very exceptional occurrence.

CHRONIC INTESTINAL STASIS.[1]

By G. R. Satterlee, M.D.,

ATTENDING PHYSICIAN TO FORDHAM HOSPITAL, CHIEF OF CLINIC FOR GASTRO-ENTEROLOGICAL DISEASES, UNIVERSITY AND BELLEVUE HOSPITAL MEDICAL COLLEGE, NEW YORK.

(From the Gastro-enterological Department of the University and Bellevue Hospital Medical College.)

Is it not necessary clearly to define the terms "stasis," "constipation," and "intestinal toxemia?" For they have been used loosely and interchangeably, much to the confusion of students of the subject. The term "stasis," from its derivation, may be an excellent one to denote areas of local stagnation in the bowel, and if thus limited it would come into general usage. Now, however, there is a tendency to utilize the term to denote the systemic condition, more properly, as it seems to us, described as intestinal toxemia. For this reason, and to avoid confusion, the author has chosen to discontinue its use, confining himself to the generic term toxemia and to the old term constipation as denoting areas of local delay in the bowel.

Chronic intestinal toxemia[2] is a diffuse intoxication of unknown origin, the result of aberrant biochemical conditions, usually, but by no means always, bearing a measurable ratio to the delay in the onward passage of the intestinal contents, as visualized by the roentgen-ray.

In considering this complex of toxemia, therefore, it is convenient, as shown in the tables, to classify them for analysis according to the areas of bowel which are locally effected. This also affords at once a working basis for rational treatment, being merely an application of the direct or objective method to the alimentary canal. This seems logical and timely, for gastro-enterologists should not

[26] Virchows Arch., 1892, cxxvii, 85. [27] Ibid., 1891, cxxiv, 373.

[1] Read before the Jefferson Medical College Clinical Society, Philadelphia, January 28, 1916.

[2] G. R. Satterlee, Chronic Intestinal Stasis, New York Med. Jour, June 12, 1915.

linger behind the genito-urinary or other progressive specialists who have long since given up the old subjective methods of diagnosis.

Regarding the etiology of toxemia very little is known, but it has been supposed that constipation was the usual exciting cause. Whether the origin of the toxemia is traceable to bacterial causes or to disturbance in the internal secretions of the gut itself is unproved, but of the two the bacterial hypothesis has rather more support than the biochemical, from our therapeutic results. Nevertheless, though many mild cases respond to a protein-free diet, graver ones usually will not, and these in turn may or may not react favorably to autogenous colonic vaccines. One thing is certain from the study of this series, namely, that congenital or acquired deformity of the gut is a strong predisposing factor.

Regarding pathology, our studies at the present are incomplete, but we have one fixed conclusion, namely, that observations to be of any value at all must be made upon the fresh postoperative tissues rather than upon dead-house material, the latter having led many observers into the gravest kind of errors on account of the rapidity of postmortem changes. It is encouraging to note that all of the developmental reconstruction cases have shown extensive as well as widely differing gross and microscopic lesions. Furthermore, some of the cases showed fresh local peritonitis and enlarged mesenteric glands, from which colon bacilli in pure culture were isolated.

Symptoms remain the dominant factor in establishing a diagnosis. And are they not familiar to us all? Rightly divided into mental, physical, and nervous, simple and seemingly isolated as these appear to be, is it not evident with our recent knowledge that we have failed properly to understand their significance and to interpret their meaning? What multitudes of sufferers from neuralgias, myalgias, neuritides, hemicranias, neurasthenias, amauroses, etc., are being maltreated for the symptom rather than for the cause. And yet how little we know regarding the greater problems of the relation of this subtle yet powerful toxemia to the more serious and better defined lesions of cardiovascular, central nervous, and genito-urinary systems, which some of the more advanced observers consider to be reflections of this fundamental bowel perversion. Comparative pathology has not advanced far enough to settle the problem; indeed, it cannot well do so, unaided by biochemistry, but the relative immunity of the quadrupeds from human lesion is significant. In considering this, does it not seem rather odd that the sigmoid, which not infrequently causes us much trouble, is absent in the quadrupeds, occurring only in the apes and in man; an example perhaps of the overspecialization of an organ frequently referred to by Lynch and Draper.

At present, however, we must be content to consider the first mentioned symptoms rather than the better recognized entities

in the relation of cause and effect to intestinal toxemia and leave to the future an explanation of its bearing upon such intricate conditions as blood-pressure and sclerosis.

In general, it cannot be too strongly emphasized that every patient presenting any of the simple symptoms above mentioned should be looked upon as essentially autotoxic until proved to be otherwise.

Classification of these cases of intestinal toxemia, according to symptomatology, is too indefinite, so I have adopted one according to the location or locations of the lesion. Neoplasms and unusual obstructions omitted, the following classification is submitted:

(*a*) Gastric delay, due to gastric atony, water-trap stomach, and reflex causes.

(*b*) Duodenojejunal obstructions, so frequently looked upon as evidence of intestinal toxemia and believed by Lane and Bloodgood to be mechanical.

(*c*) Ileocecal obstruction and non-obstructive ileal constipation.

(*d*) Chronic appendicitis.

(*e*) Cecal dilatation and constipation.

(*f*) Atonic constipation of the colon, especially of the transverse portion. (Under here may also be grouped the dubious so-called spastic constipation.)

(*g*) Sigmoid constipation.

(*h*) Lesions of the rectal outlet.

(*i*) Combinations of these forms.

We do not as yet seem to have reached the point where there is uniformity in radiographic work, so the character and amount of the bismuth and barium meals used in these cases are as follows: For the bismuth meal, 96 grams of bismuth subcarbonate in 960 grams of fermented milk; and for the barium meal, 150 grams of barium sulphate, 32 grams of cane sugar, 32 grams of flour, and 32 grams of cocoa were used. The barium meal is more palatable and is of the same value in radiography. In all cases a bismuth or barium colon injection is given after the colon is emptied of the first meal by enema, radiographs taken immediately and twenty-fours after for "residues." Every other consideration fades before the all-important problem of diagnosis. It is well to have clearly in mind the relative value of the data upon which this is to be based. First is the subjective history; second, the roentgen-ray; third the objective history; fourth, the laboratory findings.

The autotoxic patient's chief complaint, as shown by the tabulated study of 136 cases, is extremely variable. In fact, its variability and its apparent complete separation from the intestinal canal are often its chief characteristic.

Constipation as a primary or secondary complaint appears in 114 cases, or 84 per cent.; diarrhea, in 39, or 30 per cent., of which number 30 gave a history of both diarrhea and constipation. In

5, or 3.5 per cent., the history was unreliable, and in 8, or 6 per cent., the bowel movements were normal. Colica mucosa occurred in 59, or 43 per cent. Flatus to a marked degree in 104, or 76 per cent. Loss of weight occurred in 80, or 60 per cent. Mental symptoms, varying from simple inefficiencies to melancholias and epilepsies, deliria and stupors, occurred in 54, or 40 per cent. Nerve symptoms, neuralgias, etc., occurred in 88, or 65 per cent.

Motility is the cardinal point gained from the roentgen-ray. The patient's intestine may be ptosed to any degree without causing any symptoms. Although enteroptosis was absent in only 30, or 22 per cent., it was probably a strong predisposing factor in their illness, as shown by therapeusis.

Gastric constipation is determined by remnants of the bismuth or barium meal six hours after ingestion. Delay on this basis occurred in 54 cases, or 40 per cent. In only one was organic obstruction apparent.

Ileal constipation, shown by retardation in the terminal ileum, was present in 3; ileal obstruction by Lane's kink was relieved by operation in 1.

Cecal constipation, or the term "residual cecum," is determined by remnants of bismuth or barium in the cecum and oral part of the ascending colon, forty-eight hours after ingestion. It was present in 58, or 42 per cent., and was apparently responsible for much of the symptomatology in these patients.

Colonic delay was determined by the same method. A duration of between forty-eight and seventy-two hours in 13, or 9.5 per cent.; of seventy-two hours or over in 75 or over 50 per cent. of the cases; in 15, or 11 per cent., the colon was emptied in twenty-four hours.

Sigmoid constipation, or the term "residual sigmoid," was considered when the sigmoid flexure failed to empty at the end of three days. It was noted in 47, or 34.5 per cent., and associated with "residual cecum" in 22, or 16 per cent., and was uncomplicated by constipation in other parts of the gastro-enteric tract in 8 cases, or 6 per cent.

The association of gastric, cecal, and sigmoid constipation was very instructive. Gastric constipation, uncomplicated and due to elongated stomachs with a long pyloric arm (12 c.m. or over), the so-called water-trap stomach, was present in 7, or 5 per cent.; water-trap stomach, with residue and intestinal adhesions, in 3; water-trap stomach with residue and obstruction in cecum, 2; water-trap stomach with residue and cecal constipation, 7, or 5 per cent.; water-trap stomach with residue and sigmoid constipation, 2; "residual stomach" with no apparent anatomical abnormality and sigmoid constipation, 2.

Gastric, cecal, and sigmoid constipation combined (normal types of stomach) occurred in 6 cases; the same due to neuroses of known etiology in 2 cases; gastric constipation with chronic appendicitis

(proved at operation) in 5 or 3.7 per cent.; gastric constipation and ileocecal obstruction, 1; gastric constipation with perirectal adhesions, 2 cases.

Of the entire series, 33 or 25 per cent. had had the appendix previously removed without lasting benefit to the chronic condition.

Our observations upon the colonic vaccines have been significant both in differential diagnosis and in therapy. Of course, the subject is undeveloped and not one permitting of dogmatic deductions. Whatever the final decision, any form of therapy which in some cases achieves great benefit to the sick and can do no harm, and which at the same time stimulates research and throws some light on questions of etiology, is a good therapy.

The vaccine is prepared in the usual way from the prevailing type of colon bacillus, isolated from the patient's feces. The dosage is of very great importance, and injections should not be given when the bowel is loaded, else an unnecessarily severe reaction is apt to result. This in itself is an interesting and perhaps significant fact. The initial dose has been from 25,000,000 to 50,000,000, continued at intervals from four to seven days, and the maximum dose 300,000,000 bacilli.

In typical cases of chronic intestinal toxemia, usually a reaction is experienced within twenty-four hours. This consists of a small, red, painful, and slightly indurated area, the size of a dime or nickel, slight headache, giddiness, or nausea, increase in the neuralgic or myalgic pains, occasionally increased peristalsis, followed by marked relief of symptoms in forty-eight hours. So far no cases in which a typical severe reaction has occurred have been free from what is considered chronic intestinal toxemia, showing the diagnostic value of the procedure. A few examples will suffice to show results. In a patient with marked enteroptosis and a chronic intestinal obstruction and attacks of vomiting of duodenal contents, vaccines alone would check the vomiting after the ordinary well-known methods had been tried. Reactions were severe, but this treatment relieved on various occasions, and the patient is still alive, declining operation.

At the present time two other patients needing but constantly refusing operation for intestinal obstruction have been kept on their feet, one for three months, the other for a year. The first patient has probably an adhesive appendicitis and is improving; the second has just been operated upon, and strong bands of adhesions across the ascending colon and adhesions of a displaced uterus to the rectum found. She had numerous physicians and different kinds of treatment for years, most of the physicians advising operation. No treatment except the vaccine gave any real relief, and she had been dependent upon the vaccine for nine months prior to operation. Several other cases of a similar type and results could be quoted if time would permit. One of the most striking results, however,

was in the case of a patient who had intestinal toxemia for years, with profound depression amounting to insanity for two years. The urine was saturated with indican and she was mentally incompetent. The colon was kinked and diseased. Developmental reconstruction of the colon was done by Lynch and Draper, but the mental condition became worse with delirium and coma, severe albuminuria with all kinds of casts, and for a week she was expected to die hourly. Autogenous colon vaccines were given followed by very severe reactions, increased delirium, restlessness, and the patient had to be restrained to the bed. These reactions lasted for from eight to twelve hours, followed by a period of calm and general improvement and a diminution of the indican and albumin and casts. Vaccines were administered every four days for a month and a half, when they were discontinued, the patient leaving the hospital weak but in good mental condition. It was then for the first time that I obtained an intelligent connected history from her. Two years after the operation she is in good physical and mental condition. I quote from the nurse's notes:

"November 4, 1914. Second dose of vaccine, 75,000,000. Slight rise of temperature, marked rapidity of pulse, extreme restlessness and slight delirium, lasting twelve hours."

Doctor's notes on November 16, the beginning of the sixth week after the operation.

"Marked improvement in the general condition and spirit; noises in the ears still present; crash of paper causes agony; can read the dial on the watch for the first time today."

Nurse's note on November 20, after the sixth dose of the vaccine.

"Difficult breathing, immediate weakening of the pulse. One hour after, pulse hardly perceptible, responded to stimulation slightly; weak and exhausted condition; lasted twelve hours."

Urinalysis: Albumin diminished, indican still in large quantity.

December 2. Ninth dose of the vaccine, 100,000,000, reaction very slight, general condition improved. Urine, no albumin, moderate amount of indican. Apparently the colon vaccine saved her life.

The exact mode of action of the colon vaccine is by no means clear. When the author began to use the autogenous product four years ago it was with the idea that at least some of these cases of intestinal toxemia were bacterial in origin and that some sort of immunity against the colon organism could be established by injecting their toxins. Three years ago Adami[3] spoke of "subinfection in auto-intoxication," and that the intoxication could be caused by bacterial ectotoxins. He says that the members of the B. coli group produce no recognizable ectotoxins; the same also is true of another important group, the streptococci. If this be true

[3] Chronic Intestinal Stasis, Auto-intoxication and Subinfection, Colorado Med. Jour., Denver, 1914, xi, 34.

the intoxication could be only through bacteriolysis, through breaking down and liberation of their split products.

It is the general consensus that vaccines are useful for the cure of local infections, but they may also be of use in some general instances. If it is true that intestinal toxemia is due in some cases to the end products of colon infection and that the infection is localized to the intestinal tract or its immediate neighborhood, immunization by means of vaccines would not be an irrational method, just as their usefulness has been recognized by some in colon infections in the genito-urinary tract or elsewhere.

The local infection by the colon bacillus in the portion of the large intestine removed at operation has been demonstrated and the bacilli recovered from some of the mesenteric lymph nodes, as already stated.

Bassler,[4] in 1910, published results of treatment of chronic intestinal putrefactions by means of rectal instillations of autogenous bacteria and strains of human Bacillus coli communis. In the literature I have been unable to find mention of treatment of this condition by subcutaneous or intravenous administration of the autogenous product.

CLINICAL HISTORIES OF THE TEN TABULATED CASES.

CASE I (on chart).—W. W. B., male, aged thirty-three years, married. Whole family is nervous, and they have "indigestion." Nothing noteworthy until seven years ago, when he had "ptomaine poisoning." Since then has been progressively constipated, with attacks of vomiting and severe eructations. In the past three years the attacks have been more frequent and more severe, lasting two weeks, with shorter intervals between attacks. Vomits food and bile, and has long strings of mucus in the stools. Appendectomy two years ago. Has lost 40 pounds, and is unable to work. Obstipation severe. Marked emaciation; vomits and eructates large quantities of gas when touched. Blood-pressure, systolic, 170; diastolic, 120. Arteriosclerosis marked. Diagnosed as chronic interstitial nephritis. Our diagnosis, intermittent obstruction in colon. Radiographs showed water-trap stomach, $3\frac{3}{4}$ inch ptosis, delay in ileum, marked coloptosis and delay in transverse colon and sigmoid.

Operation. Loose typhon and volvulus formation. Reconstruction of colon by Drs. Lynch and Draper. Slow recovery aided by colon vaccines, but well and at work in two years; blood-pressure returned to normal. Is naturally careless.

CASE II.—C. B. Insanity, with marked intestinal toxemia. Described previously; reconstruction of colon; toxemia cleared up by colon vaccines.

[4] Bassler, A., Med. Record, September 24, 1910.

CASE III.—M. D., female, aged twenty-seven years, married. Her sister has a similar gastro-intestinal condition. Eight years, following the birth of the first child, severe constipation, occasionally colica mucosa, and diarrhea. Headaches, pain in eyes, vertigo, occasionally vomiting and hemorrhoids. Flatulence marked, with difficulty in passing gas per rectum. Dragging sensation in the lower abdomen and pain in the right lower quadrant. Medical treatment for gastro-intestinal condition for four years and ventral suspension of uterus one year ago. No improvement. Lost 12 pounds. Examination one year ago showed toxic appearance, marked enteroptosis. Radiographs showed enteroptosis and residual cecum.

Operation. Reconstruction of the colon for a loose diseased organ. After treatment: abdominal support and autogenous colon vaccines. Complete recovery within one year.

CASE IV.—R. B. E., female, thirty-three years. As a child undeveloped and "poor assimilation." Always constipated with attacks of colica mucosa. Numerous operations; gangrenous appendicitis, cystic ovary, displacement of uterus and adhesions, torn perineum and sepsis following childbirth. Also for gall-stone and adhesion of gall-bladder to colon.

Neurasthenic, neurotic, and melancholic to an extreme degree. Christian Science and hypnotism of no help.

Radiographs showed enteroptosis, marked residue in cecum and sigmoid, which was enormous. Reconstruction of the colon, with slow recovery, aided by colonic vaccines. Secondary operation for obstruction at operation site followed by ultimate recovery.

CASE V.—C., female, aged thirty-eight years, married. Family history of migraine. Possibility of luetic infection, with one positive Wassermann reaction. Three doses of salvarsan and mercurials; temporary relief of symptoms and negative serum and spinal fluid reactions. Series of severe headaches, vomiting, constipation, and hemorrhoids. Flatulence, but no gas, passed per rectum. Symptoms began after birth of child fifteen years previous. In bed the greater part of the time. Lost 40 pounds. Improved for a year and symptoms became worse with severe pain in region of gall-bladder. Radiographs showed "residue" in cecum and three days bismuth in colon.

Laparotomy. Gall-bladder normal with small adhesion to colon. Cecum and ascending colon enormously dilated; duodenum also dilated; practically a volvulus formation. Reconstruction of the colon. Recovery and patient passed gas by rectum "for the first time in twelve years." Return of headaches one year later with evidences of cerebrospinal fluid pressure but these disappeared and patient is well three years after operation; gained 50 pounds.

CASE VI.—H. R., male, aged twenty-five years, married. For eight years had constipation, frequent attacks of pain in right iliac region and nausea after eating. Extreme tenderness in right lower

quadrant, palpable and crepitating cecum. Diagnosis of appendicitis and residual cecum and sigmoid. Stomach was normal; no enteroptosis.

Operation. Cecum and ascending colon chronically inflamed and covered with fibrinous flakes; long appendix, inner third bound down by firm adhesions; enlarged mesenteric glands. Partial reconstruction of colon and hemorrhoidectomy. Recovery, with normal bowels, three months after.

CASE VII.—W. L. R., male, aged thirty-five years; married. Father died with a hemorrhage from the stomach; mother with carcinoma uteri. History dated from five years ago, following severe mental strain, and symptoms have consisted chiefly of extreme nervousness and "obsessions." He was unable to enter a strange place to eat or to go into a room where strangers were or to leave the same. Sensations of strangulation and faintness, and practically unable to conduct his own business. Markedly enteroptotic, gurgling, and crepitation over cecum. Radiographs showed residual water-trap stomach and cecal constipation. Feces showed excessive fermentation and putrefaction. Two years' treatment by a competent neurologist, with no particular attention to the gastro-intestinal tract, had given no improvement. Medical treatment for intestinal toxemia, with abdominal support and diet and colon vaccines, resulted in marked improvement in less than six months.

CASE VIII.—J. F. S., female, aged forty-five years; married. Daughter has a very similar condition of the gastro-intestinal tract. For years patient had had severe constipation, progressive neurasthenia, flatulence, loss of weight, abdominal discomfort (feeling of "drag"), headaches, and neuralgias. For past year vomiting, with purging and chills. Markedly enteroptotic. Radiographs showed water-trap stomach with five-inch drop and large residue at six hours. Cecal constipation and sharp angulation at hepatic flexure. Long sigmoid.

Operation. Coffey suspension of colon with Beyea shortening of the gastrohepatic ligament. Recovery gradual, aided by abdominal support, antitoxic diet, and colon vaccines. Three years after was well, except for slight intestinal toxemia, and gained 20 pounds.

CASE IX.—B. R., female, aged forty years; single. No family history of intestinal trouble. A year and a half ago her bowels began to be loose, with pains in the stomach and in the right inguinal region. Since then diarrhea, alternating with constipation, and for the last six months stools were hard and ball-like, covered with mucus. Lost 30 pounds. Markedly enteroptotic. Gurgling and crepitation over cecum and tenderness over whole colon. Water-trap stomach, with large residue at six hours. Treatment for the enteroptosis and intestinal toxemia improved patient much at first, but on account of the continual pain and tenderness in the appendicular region the diagnosis of chronic appendicitis was made and

operation advised. This was finally done by some other physician, but the symptoms have not cleared up, probably because of lack of proper medical after-treatment.

CASE X.—R. C. D., female, aged thirty-four years; married. Eight months' baby; weak and did not walk until three years. Fell on the ice when fifteen and had a retroversion since then. Appendectomy for ulcerative appendicitis at that time. Complete breakdown since then, with headache, backache, lack of mental concentration, and coördination. Stomach trouble and constipation since childhood and numerous "bilious attacks." At seventeen severe obstipation and no movement for thirteen days. Ten years ago, hematemesis. Markedly toxic; excess of food remnants; fermentation and putrefaction in feces; excess of indican in urine. Radiographs showed no enteroptosis but marked cecal constipation. Uterus retroverted and fixed. Medical treatment for intestinal toxemia was diet and mineral oil and colon vaccines, the latter giving the most help.

Operation, January 1916. Strong bands across ascending colon severed and adhesions of uterus to rectum relieved and redundant portion of cecum removed. Recovering. Noteworthy was the good result from the autogenous colon vaccines.

The writer wishes to express his gratitude for the valuable assistance of Dr. Arthur Mandel for the clinical pathology, Dr. Albert G. Bennett for the bacteriology, and Drs. Leon T. Le Wald and John W. Draper for the radiographic work. To Drs. J. M. Lynch and John W. Draper he is deeply indebted for the opportunity to study the operative side and for their operative skill on his cases. Dr. John Douglas and Dr. Burton J. Lee have also operated on some of the patients.

It would scarcely be proper to close without mentioning the character and number of operations in this series of cases. There were 31 abdominal sections. Appendectomy, chronic or subacute, 9; colon suspension, 9; for reconstruction of the colon (Lynch and Draper), 8 (all recovered except one with advanced toxemia and toxic arthritis, who died with a septic peritonitis); ileostomy, 1; colon suspension, appendectomy, cholecystectomy, and adhesions, 1; plication of cecum, 1; colon suspension and nephropexy, 1; gastroenterostomy and Lane's kink, 1.

In conclusion, it is evident that the closest kind of coöperation should exist between the physician and surgeon, as no real internist should fail to be a student of actual conditions.

The view-point should be neither surgical nor medical in the old sense, but should be critical and unbiased by old dogmatic views. The cure of the patient should not end with the operation. Most of the failures in the past have been due to lack of coöperation between the physician and surgeon, and often caused by the improper following up of the patient.

CHART OF TEN CASES PRESENTED IN DETAIL.

Patient.	Roentgen-ray findings.					Bands.	Congenital anomaly; remarks.	Sex.	Age.	Bowel history.				Feces, excess of			Symptoms.							Previous operations.	Treatment.			Results.
	Enteroptosis.	Residual stomachs.	Residual cecum.	Residual sigmoid.	Colon empty.					Diarrhea.	Constipation.	Regular.	Colic mucosa.	Food remnant.	Putrefaction.	Fermentation.	Indican, urine.	Mental.	Physical.	Nerve.	Flatus.	Loss of weight.	Crepitation of cecum.	Preventive appendectomy.		Operative.	Medical.	Colon vaccine.	
W. W. B.	+[3]	0	+	+	3d+	Volvulus	High blood-pressure	♂	33	−	+[3]	−	+	−	+	+	−	+	+[2]	+[3]	+[3]	40	+	+	−	Reconstruction of colon	+	+	Well (3 years); blood-pressure, normal; nature careless.
C. B.	0	+[2]	+	?	?	Ileal kink	Insane; severe toxemia	♀	32	−	−	+	−	−	+	+	+[3]	+[3]	+[3]	+	+[2]	?	?	−	−	Reconstruction of colon	+	+	Well (2 years); toxic nephritis disappeared.
M. D.	+	+	+[2]	−	2d+	...	....	♀	27	−	+[2]	−	−	Not exam.			+	−	+	−	+	10	+	−	Suspension of uterus	Reconstruction of colon	+	+	Well (1 year).
R. B. E.	+[2]	0	+[2]	+[3]	3d +[2]	...	Melancholia	♀	34	−	+[2]	−	+	Not exam.			+	+[3]	+	+[2]	+	+	+	+	Ovarectomy; peritoneal adhesions	Reconstruction of colon	+	+	Improved (16 mos.).
C.	0	0	+	0	3d+	...	Volvulus; migraine	♀	38	+	+	−	−	Not exam.			+	−	+[2]	+	+[2]	40	?	−	Currettage	Reconstruction of colon	+	+	Well (3 years).
H. R.	+	−	+[3]	−	3d	...	....	♂	25	−	+[2]	−	+	Not exam.			−	+	+[2]	−	+	5	+	−	−	Reconstruction of colon	+	−	Well (3 mos.).
W. L. R.	+[2]	+	+	−	3d	...	Obsessions.	♂	35	+	+	−	−	+	+[2]	+[2]	N	+[3]	−	+	+[2]	0	+	−	−	−	+	+	Marked improvement (6 mos.).
J. F. S.	+[3]	+[2]	−	+	?	...	Similar condition in daughter	♀	45	−	+[2]	−	−	Not exam.			+	+[2]	+[2]	+[2]	+	22	+	−	R. nephropexy	Suspension of colon	+	+	Well (3 years); slight constipation and toxemia; gain 20 pounds.
B. R.	+	+[3]	−	?	3d	...	Chronic appendicitis	♀	40	+	+	−	+	+	0	0	N	−	+	+	+	30	+[2]	−	....	Appendectomy	+	+	Improved medically; Well 6 mos. after operation.
R. C. D.	0	0	+[3]	?	?	Across ascending colon	Perirectal adhesions; retroflexed uterus	♀	34	+	+[2]	−	+	+[2]	+	+	+[2]	+[2]	+[3]	+[3]	+[3]	3	+	+	....	Hysterectomy; adhesions and bands	+	+	Improved by vaccine and operation 5 (wks.).

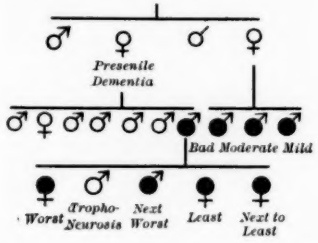
What conviction is uppermost from this study of 136 cases? Unquestionably that diagnosis is the all-important factor. Obviously this cannot be made either simple or sure until much more is known regarding the cause of intestinal toxemia. Most to be desired is a unified effort from the medical clinic, from the operating room, and from the laboratory. In this way only shall we find all of the truth.

A FAMILY WITH MYOTONIA, PROBABLY INTERMITTENT FORM OF THOMSEN'S DISEASE.

By Noxon Toomey, M.D.,
PHILADELPHIA, PA.

The following cases illustrate a myotonic family. They are interesting because Thomsen's disease is rare and very few cases of the intermittent form have been reported. Whether acquired myotonia, paramyotonia, Gower's type, myotonia with atrophy, and intermittent myotonia are forms of Thomsen's disease is not known. Recording forms met with may eventually throw light on their relationship, and it is to help to that end that this paper is compiled. Due to a lack of facilities no attempt at a pathological study has been made. The case histories were obtained with few if any leading questions, and are really narrations by the sufferers. Catch questioning elicited no contradictions.

The cases are eight in number and are in three generations. Three cases in a collateral line could not be seen by me. In the three generations there were nineteen persons over one year, thus about 40 per cent. of the family was affected. Those who have married have had large families, most of their children growing to adult age. No evidence of syphilis or rheumatism can be found in the family. The accompanying figure shows the involved collateral line. The black figures indicate the members affected.



The cases studied are in an industrious, self-respecting family of well-marked Irish descent. The family is of the unskilled labor

class but the members are intelligent and always have had more than the necessities of life. Except for the dystrophy, they have been free from sickness and are otherwise well developed and nourished. They live in South Baltimore, but come from the country. Their house is of two stories with fair light and air and good plumbing, heat, and dryness. The neighborhood is not congested.

The three cases not seen by me were described by the head of the family that I studied. My informant grew up with his cousins and knew their condition well. Their cramps were just the same as his, except that the older two had it worse than he did. The three "always had the trouble." In the oldest the condition is getting worse. The other two died of a chronic pulmonary disease after middle life. Their myotonia did not get worse after early manhood. "They did not have it as bad as their older brother, and the youngest of the three had only a little trouble in walking. The oldest brother had it so bad that he often could not walk and they would often have to go out in the field to bring him in. The next youngest could hardly walk at all when he had it." The myotonia in the three was transitory, as in the five cases that I saw.

In the cases examined the father has had it as bad as any of his children. Of the children the oldest has had it the worst. The second oldest is not affected. The next, Martin, has it worse than the youngest children, Rose and Agnes. There are three children dead, one of pertussis at seven months; the next at four months, cause unknown; the third was a two months' abortion. There are no mental peculiarities, temper, etc., in the family, and no evidence of tuberculosis, syphilis, rheumatism, neoplasms, or hysteria. Labors were all normal.

Father, aged forty-four years. Mother was "weak minded after she was fifty-five years old." Paternal side normal. Has been well except for measles, pertussis, mumps, and dystrophy; has never worked around lead, etc. Married at twenty-five. Was a street-car motorman for six years; gave up job for family reasons. Since then has worked at various moderately hard manual jobs in open air. Food and habits negative, except wife says "he is a great eater and a great one to salt his food." Drinks beer occasionally; never drunk. He says: "When I drink more beer than usual it makes my condition better."

Present Illness. "Was fourteen years old when I had first spell. Was playing base-ball one winter evening. Came home overheated. Later went to bed and slept naturally. Next morning I woke up and found I could not move myself from waist down. Could not get out of bed alone. I had great difficulty in making legs move, but could move them by great effort by end of first day. I had no pain, fever, or other discomfort. The legs got better the more they were moved, and in two or three days use of legs was regained. Second attack was about one year later, and was the

same as first. As I grew older they came closer together; some years I would have four or five attacks; sometimes twice in same month; sometimes not for six or nine months; no regularity at all. Were more frequent from my fifteenth to twenty-second year, then stayed about the same until I was thirty-five years old. In this time I would average about four or five times in a year. Stiffness would last four or five days. About every two months I would have slight attacks lasting a day only; all spells lasted a day or more. Fourteen years ago I was laid up for eleven days, in which I could move my legs but very little. For past eight or nine years they have not been coming as often and are not so long or hard."

Description of cramps: "I have not the least idea what causes them. Spells come on with no warning at all; mostly during sleep. We often talk about the cramps, but it has had no effect in producing them. I get them in hot weather as well as cold. They come on with drawing up of the belly, but no real pain. I wake up and find I cannot get out of bed for a while because my legs are stiff and will not move. The muscles never get hard for a time, but they feel too short to stretch out leaders. Even now if I sit down for three or four hours I will not be able to get up at first or will get up feeling very stiff in the legs, which must be walked off by a few minutes' exercise. When sitting still for some time I get jammed up a little and get stiff, but pay no attention to it; but get a cane and walk it off by moving around the room. I have often gone to work feeling stiff, but could stand on feet all right; but I would not have worked those days if I would have had to walk much. Sometimes during the day the stiffness would not get better by standing and I would have to walk stiffness off. I would never get worse during a day at the motor, but sometimes I would feel very tired. When I worked the day out I would feel better at night than in the morning. The longer I worked the better I felt, and the better I could move myself. During a spell I cannot take long steps at first and can only move slowly. The calf of my legs seem stiffest, and is harder than other places. Sometimes when I have been reading for a good while, when I start to look up I find my eyelids will go up but my eyes cannot; they will stay looking at the paper for a few minutes even though I want to look up, or if I want to look down my lids will not go down with my eyes. Sometimes when I want to let go of a thing I cannot do it for a moment my hand being clenched tight."

The leg muscles are affected the oftenest, the external ocular muscles next most frequently, and the hands the least. Abdominal muscles seem to be involved in some attacks. As to treatment he said: "My legs never lose color or are cold. Rubbing them with camphorated oil or anything else has never made them better, and I have found that nothing will help me except to walk stiffness off."

Physical Examination. Habitus, frame, and panniculus good. Muscles well developed, particularly of lower extremity, but are not hypertrophic. Strength in proportion. Pupillary reactions, arteries, and functional capacity of heart normal, no organic lesion. Teeth in poor condition but physically is otherwise negative. Gait and station, muscle sense, and sensation to touch and pain normal. Reflexes active and equal on two sides; no abnormal reflexes. There is no ataxia, astereognosis, trophic changes, etc. Electrical stimulation of muscles and ulnar nerve normal. Arm and leg muscles do not react to light tapping but marked percussion produces a quick, quite hard contraction that lasts from four to eight seconds. The contraction disappears gradually lasting longest in the belly of the muscle. Percussion of peronei, extensors of the hand and occasionally hamstrings and rectus femoris produces a distinct grooving of skin lasting a few seconds and a quick extension (or flexion) that is well sustained, at least six seconds elapsing before the fingers, foot, etc., return to former position. Reflex contractions do not cause cramps. No muscles atrophied.

Katheryn F., aged eighteen years. Past history unimportant. Development and puberty normal; leads moderately active life. Habits negative except prefers salty foods. Had worked as a bottle-filler for the past three years.

Present Illness. "First spell occurred at two and a half years; it lasted about a week. Consisted in legs getting so stiff when she tried to walk that she would fall down, particularly going down stairs. Left side was weaker, so that she could not stand right, but that got better right along. After first attack spells came on at night only; she would be so stiff in legs in morning that she could not get out of bed. I used to rub her legs, then she could move them a little, and after that the more she moved them the less the stiffness became. She used to have two spells a month up to five years old; would have them in hot weather same as cold. Spells of morning stiffness were all the same; they would last three days, first two days she would be helpless. Some were accompanied by nausea and fever and usually costiveness, but never looked sick enough to be the way she was." Was never unconscious, and had no ataxia, twitching, pain, or paresthesias, etc. "After sixth year had spells quite irregularly every six months to a year. Spells were the same as before, but were not so hard; they then kept on getting better. She has had no stiffness in her limbs for past five years, except three weeks ago, but has had attacks in her hands, eyes, and neck. She soon learned that the more she walked the better the cramps in her legs got."

Description of cramps by patient: "In cloudy weather come oftenest, have had two or three spells of stiff neck or right arm for many years. Stiffness lasts five minutes. While neck is stiff it pains me terribly; can move neck a little but it swells out and gets

hard. When I would rub it and move it around it would go down. Each time I moved neck the stiffness got better. Sometimes neck is stiff in morning but I think it is because I lie crooked. When neck is stiff it is only one side at a time. The left side was always the worse.

"Once a month or so I have stiffness in eyes, so that when I have been reading for some time and want to look up my lids will go up, but the eyeballs will be glued down and I cannot move them up, or sometimes when I am looking up and then look down the upper lids will not come down, but will separate from the eyes. Stiffness may last a minute. When I sometimes try to grab on to a thing quickly some of my fingers get so stiff that I cannot hold on. Only one finger draws up at a time, usually the index finger; both hands are affected equally. Not started by a hard squeeze. Fingers are never drawn back (hyperextended).

"For several years I have had cramps in the legs that draw up my toes; sometimes only the big toes; toes become stiff, and it hurts me in the hollow of my foot. Both feet are affected the same. The only stiffness in upper limbs that I have had for five years was three weeks ago, and I think it was brought on by sitting still for four hours. I was feeling perfectly well and stood up without trouble, but when I started to take the first step I found I could not; the legs were so stiff I could not straighten them out. The legs felt as if the muscles were cramped up and not long enough to stretch out the feet. It hurt a good deal. Each step I took the better the stiffness got, but it was not completely gone for two weeks. Every time I would sit still for some time it was the same thing over again; I could stand up all right, but when I walked the muscles were hard and not long enough to stretch out, so I had to walk real slow and take small steps. At first it was worse in one leg, and I had to limp for a short time. I am certain that during those two weeks I was always stiffer after sitting still a little, and the more I would walk the better the stiffness got. I have never noticed the arm and neck or legs and neck affected at a time. The attacks are not like when your foot goes to sleep."

Physical Examination. Habitus normal; musculature above average, but not hypertrophic. Strength in hands and legs less than was expected. Complete physical examination not permitted. Sensation and reflexes in extremities; gait and station normal. Nerve reactions normal. Faradic excitation and percussion of muscles of extremities produced a slow tonic contraction, lasting four to six seconds. With galvanic current, kathodal closing contraction not quantitatively reduced. Current not strong enough for kathodal opening or anodal contractions. No muscles atrophic or paretic.

John F., aged seventeen years. Chorea at eight years. Has never had myotonia. "Is the only child that resembles mother's family, which he does decidedly, being red-haired like them." Is

thought to have frozen hand. During cold weather the past four years the right hand will become perfectly white distal from metacarpus. During the attack, which lasts a variable time, there is almost complete anesthesia and analgesia. There may be paresthesias as ischemia wears off. Physical examination is negative. Muscle reactions are normal.

Martin F., aged eleven years. Past history and habits negative. "Is a great one to salt food. Stiffness began when he was five years old. Used to average about two spells a month; would be only of a few minutes to an hour's duration. Spells come irregularly; he is getting a little better of late. There has been no noticeable change (in clinical course); legs, arms, and neck muscles have been involved about equally for a number of years. The muscles in the back of his legs usually get harder than the other muscles, but when he has it in his neck the muscles stand out like two boards. When his legs get so stiff he cannot walk I rub them with liniment or camphorated oil, but I have found that hot water does as well as anything. When he is in a stiff spell he has to drag his feet after him for a minute, and when he goes up stairs I have to support him up the first steps and sometimes the whole way."

Patient says: "I do not have it much in hot weather; had only one spell last summer; when I go out in dampness it brings it on. When I sit still and sometimes when I come into the house the stiffness comes on. Then I have a hard time in getting up and usually fall; but sometimes I do not. Most of the times it makes me stiff in the legs and sometimes in the legs and arms, so I fall easily. I guess I have to go about ten steps before stiffness gets better. Rapid walking has never brought it on. I cannot always walk fast, but when I can I am always at my best. It comes on usually when I stub my toe, and then I usually fall because my legs become as stiff as sticks. Up to about a year ago I used to often wake up stiff in the morning and would have to kind of roll out of bed, then get a stick and walk around the room a few minutes. My neck gets stiff mostly when I look around quickly. When I am stiff the muscles get hard, but only the neck muscles stand out any, sometimes for ten minutes. When I grip anything real tight pretty often I have to hold it for about ten to fifteen minutes before I can let it go, but my hands never get white like John's."

Physical Examination. Well built, with good muscular development and strength in proportion. General physical negative except for several carious teeth, adenoids, and slightly enlarged tonsils and cervical glands. No thymus dulness. Sensation, etc., normal. Reflexes quite active but equal; no clonus or abnormal reflexes. Gait normal. Muscular reactions: light percussion causes slight contraction of belly of muscle. Heavier percussion of extensors causes a slow contraction lasting four or five seconds, followed by a slower relaxation. Percussion of peronei causes a sustained ever-

sion of foot. Hard percussion two inches above patella causes a slow extension of leg, followed by an equally slow flexion by gravity. Faradic and galvanic stimulation normal. Blood picture: normal. Urine: normal except for sp. gr., 1.008 to 1.010, two specimens. Von Pirquet negative.

Rose F., aged nine years. Well except for measles and tonsillitis past three years. Mother believes the stiffness comes with the tonsillitis, which is febrile and accompanied by dysphagia and anorexia. "She has had it less often and lighter than the others, and it does not last as long." Patient says: "I have had disease about two years; spells have not come as often this year as they used to. In December, 1914, I was in school and my legs got so stiff I could not walk, the stiffness lasted half an hour. Two months later I suddenly got stiff at the head of the stairs and had to be carried down them. The stiffness lasted ten minutes, then I walked around and got better. From then until December 24, 1915, my legs have been stiff once, arms stiff twice, and neck stiff once. December 24, 1915, had stiffness from knees down, lasting fifteen minutes. January 5, 1916, neck was so stiff that it could not be moved for about five minutes. During attacks right side is often stiffest. The muscles do not get real hard, and spells never hurt at all. When I feel my legs get stiff I have to get up and walk slowly and take little steps, which make it go away quicker, but stiffness usually gets better of a sudden. About two hours after I have a spell Martin and Agnes will have the same stiffness." Rose has had no paresthesias, trouble in standing, no stumbling, falling, involvement of ocular muscles, etc.

Physical Examination. Frame and panniculus good. Musculature fairly well developed, strength equal. Slightly enlarged tonsils, no adenoid enlargement. Cervical glands barely palpable, indurated. Thyroid normal, no thymus dulness. Functional capacity of heart and lungs normal. Abdomen and remainder of examination negative. Blood picture normal except for hemoglobin, 75 per cent. (Sahli). Urine (several specimens) normal except for heavy amorphous urate cloud on admission to hospital. Wassermann and von Pirquet negative. Took ether well; developed no acetone. Nerve reactions normal. Muscle reactions: studied during an attack of myotonia. Child was found sitting on edge of chair with thighs extended, due to difficulty in overcoming hamstring spasm. Legs flexed, toes extended, but less rigid. Whenever asked to walk she slid off chair sidewise and attained erect attitude with some difficulty. She limped at first, due to left leg being more strongly flexed. The steps at first were slow and manifestly difficult, but not greatly shortened. There was no pain or adductor spasm. After seven or eight steps the spasm gradually broke and the patient gained a normal gait, precluding spinal syphilis. Thigh and leg muscles were hard, and firm pressure made them much

harder than the arm or trunk muscles. Passive muscular movement and reflex contraction normal and excited no myotonia. Marked percussion of unaffected muscles produced a slight myoidema; harder percussion produced a slow contraction lasting about eight seconds. Light percussion of the affected groups, the hamstrings and quadriceps, produced myoidema. Moderately hard percussion of rectus femoris and bellies of vasti produced a slow extension of the leg that lasted ten seconds before being gradually flexed by gravity. Hard percussion of hamstrings produced a tonic contraction lasting ten seconds to an hour, and during a light ether anesthesia they could be felt as hard cords. Hard percussion of hamstrings produced a grooving of skin instead of a mounding. The myobradia was most marked in the rectus femoris. No paresis or atrophy of any muscles.

The unaffected groups were less excitable to faradic stimulation than normal. They were slightly hyperexcitable to kathodal closing, but anodal closing was not obtainable. The affected groups would not contract to strong faradism. In these muscles a thirty-volt wave-free galvanic current produced on kathodal closing a slow tonic contraction that lasted about a minute after cessation of stimulation. Anodal closing contractions were nearly as strong as the kathodal. Opening contractions not obtainable. The attack of myotonia lasted about six hours and then disappeared quickly. During the six hours the thigh muscles were somewhat less hard after walking about wards, only to become stiff after a few minutes' rest.

Agnes F., aged six years. Past history and habits unimportant. "Has had no sore throat and has not been sick when she has had the cramps. She has had the trouble past three years, is not getting worse. First noticed drawing up of all fourth fingers and toes. Spasms will last two minutes. Are noticed mostly at breakfast table; will average two or three cramps a week. I think Agnes gets it mostly in cold weather; her arms are mostly affected, then her legs, then her neck. She is clumsy and stumbles easily; she falls frequently, particularly down steps. If she would glance around quickly her eyes would get so stiff that she could not shut them. When Agnes gets stiff in her legs she trys to stand up and walk. Sometimes she falls at first and may need holding for the first few minutes, but after she gets walking around a little she gets better and then is shortly all right. When she has the cramps she has no pain at all, but muscles get hard, particularly when she has them in the neck; then the muscles will stand out like boards. If I walk her fast she gets spasms in her muscles and cannot move her legs right; coming up here, when I walked her fast, she got stiff in her legs and I thought we would never get here. She had to take slow, short steps, but after walking some the spasm went away and she walked all right. She has it oftener than the others, but not as bad

as Katheryn, may be because the child is never still the whole day, but is always on the go."

Physical Examination. Strong, well built, and nourished. Hemoglobin and blood picture normal. Small adenoids; tonsils slightly enlarged. Uncorrected hypermetropia of about D. 2. Thyroid normal; no thymus dulness. Von Pirquet negative. Knee-jerk obtained with reinforcement, equal; sensations, etc., normal. Electrical reactions, gait, and station normal. Percussion of extensors, but more particularly flexors, produces a grooving of skin and a slow movement of digits. Fingers are maintained in flexion (or hyperextension) for about fifteen seconds before returning to previous position.

LITERATURE.

Nearly three hundred articles on Thomsen's disease are listed in the Catalogue of the Surgeon-General's Library and the later volumes of the Index Medicus. About four hundred cases have been reported, mostly cases with constant myotonia and of the hypertrophic and atrophic types.

Metabolism studies are recorded in Am. Jour. Med. Sc., vol. cxli, and Arch. Int. Med., August, 1914.

Some of the other important articles consulted are in: Quart. Jour. Med., April, 1910, January and July, 1912, January, 1915; Edinburgh Med. Jour., N. S., vol. xi; Montreal Med. Jour., vol. xxxvii; Allbutt's System; Osler's Modern Medicine.

The following treat of the intermittent form:

Erb. Die Thomsen'sche Krankheit., Leipzig, 1886.

Pelz. Arch. f. Psychiatrie, vol. xlii.

Martius und Hansemann. Arch. f. path. Anat., etc., vol. cxvii.

Mingazzini e Perusini. Rev. d. patol. nerv., vol. ix.

Lord. Boston Med. and Surg. Jour., vol. cxlii.

REVIEWS

PROGRESSIVE MEDICINE. QUARTERLY DIGEST OF ADVANCES, DISCOVERIES AND IMPROVEMENTS IN THE MEDICAL AND SURGICAL SCIENCES. Edited by HOBART AMORY HARE, Professor of Therapeutics, Materia Medica, and Diagnosis in the Jefferson Medical College; Physician to the Jefferson Medical College Hospital, Philadelphia, etc. Assisted by LEIGHTON F. APPLEMAN, M.D., Instructor in Therapeutics, Jefferson Medical College, Philadelphia, etc. Vol. I, March. Pp. 354; 19 illustrations. Vol. II, June. Pp. 482; 113 illustrations. Vol. III, September. Pp. 394; 18 illustrations. Philadelphia and New York: Lea & Febiger, 1916.

THUS far during this year there have appeared three volumes of this well-known and justly popular quarterly review of medical progress. The March number opens with a discussion of the surgery of the head and neck by Charles H. Frazier. Most of his attention is directed toward the cranial nerves and the brain. The article concludes with a section devoted to the mammary gland. A most interesting and instructive article on the surgery of the thorax has been contributed by George P. Müller, who devotes a large proportion of his article to a discussion of empyema. The longest article in this volume, as well as one of the most enlightening, is John Ruhräh's contribution on infectious diseases. Over 120 pages is devoted to this all-important and comprehensive subject. A great deal of work during the past year has been done upon the infections, and Ruhräh's article is replete with instructive suggestions and observations. The subject of diseases of children is taken up by Floyd M. Crandall in about 30 pages. As usual, the diarrheas of children and the dietetic problems of infancy receive considerable attention. George B. Wood furnishes the review of rhinology and laryngology, devoting particular attention to the accessory sinuses and tonsils. A short review of otology by Truman Lawrence Saunders concludes this volume.

Volune II opens with a 34-page article by William B. Coley on hernia. This is followed by a thorough discussion occupying 146 pages of the surgery of the abdomen by John C. A. Gerster. He lays stress upon the timely subject of gunshot wounds of the abdomen in war. Various affections of and operations upon the stomach, duodenum and small and large intestines are then taken up in order. He devotes great care to a review of recent work upon the liver and

bile passages, and concludes his article by a discussion of the surgery of the spleen, a subject which has recently attained considerable importance. Under gynecology John G. Clark furnishes his usual interesting, complete, and valuable contribution. He again accords cancer of the uterus first place, although non-malignant conditions of the uterus are also discussed with unusual thoroughness. Alfred Stengel covers a wide range of important medical subjects in an article of 122 pages. Diseases of the blood are first taken up, and the spleen and hemorrhagic diseases are then discussed with a thoroughness justified by the importance which these conditions have recently assumed. In addition to the thyroid and parathyroid glands it is gratifying to note the space which is devoted to a consideration of affections of the pineal gland. He concludes his article by a thoroughly up-to-date review of diabetes and gout. The last article in the volume is by Edward Jackson on ophthalmology. In this the affections of the eye are taken up under the various anatomical divisions of the organ.

The third volume, which appeared but a few weeks ago, contains an article by William Ewart on diseases of the thorax, including the heart, lungs, and bloodvessels. Ewart enters first into an instructive review of the respiratory function. He then discusses a number of interesting recent observations upon physical signs and methods of physical diagnosis. Next, he takes up pulmonary tuberculosis and various respiratory and pulmonary affections. Much important material is reviewed under the subjects of the blood, the bloodvessels, and the circulation, among the most interesting of which are the "soldier's heart," various unusual diatheses and syndromes, vagotonia, shock, and "heart seizures." As usual, William S. Gottheil's contribution on dermatology and syphilis is decidedly enlightening. Autoserum therapy, heliotherapy and pellagra are some of the subjects particularly dwelt upon. His contribution on syphilis is especially worthy of note. Edward P. Davis gives a comprehensive review of recent advances in obstetrics. Pregnancy and the toxemia of pregnancy occupies a large portion of his contribution. The placenta, the puerperal period, labor and its management, obstetric surgery, and finally the newborn are all dealt with in detail in the course of this unusually long article of nearly 200 pages. The final section of the volume is a scholarly contribution by William G. Spiller on diseases of the nervous system, in which he lays particular stress upon the subject of brain tumor, cerebrospinal syphilis, syringomyelia and many other important complicated neurological subjects.

A comparison of these three volumes of *Progressive Medicine* leaves little to choose. In every instance the contributions are furnished by men of acknowledged prominence in their respective fields, and throughout the preparation of the articles has been conducted with praiseworthy care. G. M. P.

OPERATIVE MIDWIFERY. A GUIDE TO THE DIFFICULTIES AND COMPLICATIONS OF MIDWIFERY PRACTICE. By J. M. MUNRO KERR, M.D., C.M. (Glas.), Professor of Obstetrics and Gynecology, Glasgow University (Muirhead Chair); Obstetric Physician, Glasgow Maternity Hospital; Gynecologist, Royal Infirmary. Third edition. Pp. 711; 308 illustrations. New York: William Wood & Co., 1916.

THE importance of the surgical aspect of modern obstetrical practice receives its full due in the volume before us. That it has reached a third revision in seven years is a measure of the advances in the art of obstetrics during this time, and none the less an unspoken commendation of the book itself. Dystocia has been considered in a most comprehensive manner from every stand-point. The operative maneuvers in delivery, and also those precedures necessitated by complicating conditions of the pelvic organs, are described in detail. The chapter on the use of forceps would be of little use to American physicians, as the performance of the forceps operation with the patient in the lateroprone position is not familiar teaching in this country. In a similar manner the illustrations portraying the use of the various models of forceps is confusing.

Extraperitoneal Cesarean section is looked upon with disfavor. The merits of the operation in presumably infected cases necessitating supravaginal delivery are overlooked, and it is judged rather by a comparison of the scar resulting in the lower uterine segment with the higher scar of the classical operation. Accidental hemorrhage, premature separation of the normally situated placenta, and in view of the pathology, intramural hemorrhages, are considered as forms of pregnancy toxemia. In order to lessen the maternal mortality from the often uncontrollable postpartum hemorrhage, the author recommends hysterotomy followed by abdominal hysterectomy. There is a well-written chapter devoted to parturitional injuries of the child. This third edition fully maintains the high standard established by its predecessors. P. F. W.

DIE THERAPIE DER HAUT: UND VENERISCHEN KRANKHEITEN. By Prof. Dr. J. SCHÄFFER in Breslau. Pp. 450; 87 illustrations. Berlin and Vienna: Urban and Schwarzenberg.

DR. SCHÄFFER'S excellent volume is divided into two distinct parts, the first, dermatological and the second, venereal diseases. The various remedial cutaneous agents are discussed under the following headings: The technic for handling various diseases; alleviating hints for the assortment of medications; the different

methods of application; salves and oils; salve bases; dusting powders; mixtures that have to be shaken before applying; plasters; varnishes; zinc adhesives; soaps; and waters.

Physical healing methods are detailed under heat applications; light therapy; surgical interference; diet; and internal treatment. After the various external and internal methods of treatment have been discussed, the writer applies the various means to the individual cutaneous outbreaks; arranging the latter diseases alphabetically.

Two hundred and eighty-five pages are devoted to dermatological conditions, one hundred and four of which are devoted to the various external applications and internal remedies and the remainder to those applicable to the individual cutaneous outbreaks; fifty-five pages treat of gonorrhea, in its various stages and complications, ulcus mollus, inguinal buboes, etc.; and seventy-six to the treatment of syphilis.

The treatment of syphilis is amplified by the technic of microscopical spirochetal investigation, serological studies, the method of obtaining the blood from the vein (venous puncture), and the clinical meaning of the Wassermann test. Syphilitic therapy is interestingly described, including the mercurial, iodide, salvarsan and neosalvarsan methods. The various procedures advocated are detailed according to the stage of syphilis that is to be treated, including the earliest and latest manifestations of the disease, the congenital form of the affection, the general hygiene of the patient, and the local therapy of various lesions.

The eighty-seven pictures in the text illustrate graphically the various methods of applying the medicaments, the injections, roentgen-ray, Kromayer lamp, dark-field illumination, the Wassermann test, etc. F. C. K.

Mosquito Control in Panama. The Eradication of Malaria and Yellow Fever in Cuba and Panama. By Joseph A. Le Prince, C.E., A.M., and A. J. Orenstein, M.D. Pp. 335; 100 illustrations. New York and London: G. P. Putnam's Sons, 1916.

The book is written in semipopular style and may be read by anyone who has an interest in the great engineering feat of constructing the Panama Canal.

The work is considered from two standpoints, as it relates to the campaign against malaria (Part I, Anti-malarial Campaign), and to the fight against yellow fever (Part II, The Yellow Fever Campaign).

The campaigns against malaria and yellow fever in the Canal

Zone were conducted by the authors under the direction of General Gorgas, and full details are given of the problems and how they were met. Mr. Le Prince had served under General Gorgas in cleaning up Havana, and the experience gained in this earlier work was invaluable in the prosecution of the more extensive and more difficult work in the Canal Zone.

Fundamentally the campaigns against the mosquitoes concerned in the transmission of malarial and yellow fevers may be divided into four principal divisions: (1) drainage of all bodies of water that could be so diverted, the construction of concrete gutters for the smaller water courses, and the removal of vegetation from the banks and the beds of the streams; (2) the application of oil to all bodies of water and to flowing streams in order to kill mosquito larvæ; (3) the screening of all buildings to protect against mosquitoes and the trapping and killing of mosquitoes that had entered the houses; (4) the general cleaning of habitations and towns.

It was a fortunate circumstance that at the time when the United States took over the construction of the Panama Canal there had developed a knowledge of the agency of mosquitoes in the transmission of malaria and yellow fever, otherwise (as the authors state) the great engineering work would have been a failure as it was under the supervision of French engineers who did not have this knowledge to aid them.

The greatest honor connected with the completion of the canal must be given to the intelligent sanitary engineers who applied the knowledge which experience had then shown to be imperative if the undertaking was to be completed without unnecessary sacrifice of human lives.

The illustrations show clearly how the important work of mosquito extermination was carried out.

This book will serve as a reliable guide to those engaged in similar work elsewhere. It is possible to rid any community of malarial and yellow fevers at a cost which will be infinitely less than that entailed on such a community by these two diseases.

D. H. B.

LEUKEMIA OF THE FOWL: SPONTANEOUS AND EXPERIMENTAL. By HARRY C. SCHMEISSER, M.D. Pp. 34; 4 plates. Baltimore: Johns Hopkins Press.

THIS monograph is an extensive and complete discussion of that interesting condition, fowl leukemia, which may be transmitted directly from one fowl to another by means of injection of an organic emulsion. The injection causes a disease similar to that which is spontaneously developed, and the changes which are produced are comparable to those which are seen in the corresponding disease of human beings.

J. H. M., JR.

GESCHICHTE DER NASENHEILKUNDE VON IHREN ANFÄNGEN BIS ZUM 18 YAHRHUNDERT. By KARL KASSEL (Posen).

THIS work of 476 pages presents the subject of the history of rhinology with the characteristic German love of detail. The author starts with the Egyptians, Assyrians, and Babylonians and their methods of treating diseases of the nose. Considerable space is given to the Grecian and Roman philosophy and medicine, perhaps in too great detail for the casual reader. Hippocrates and Galen, of course, are given great prominence. The middle ages start with the Arabs (608 A.D.) and end about 1500.

The third chapter on the later times (Neuzeit) begins with Paracelsus and continues to the seventeenth century.

The work will never find general popularity on account of its minutiæ, as it is practically an encyclopedia on the subject, but will probably be the standard reference on the history of rhinology for all time. G. M. C.

VIEWS ON SOME SOCIAL SUBJECTS. By SIR DYCE DUCKWORTH, Bt., M.D., LL.D., Fellow and Treasurer of the Royal College of Physicians, London; Consulting Physician to St. Bartholomew's Hospital. Pp. 320. New York: The Macmillan Company.

THESE essays represent the views and impressions that a medical man has gathered during the greater part of a lifetime, a lifetime devoted for the most part to the practice of medicine, but broad enough to consider and to engage in other activities. As their titles imply, they represent views of social subjects, most of which have some relationship to medicine, though a few have no connection whatsoever with medicine. They will well repay the reader in the delightful hour that they will give. J. H. M., JR.

INFANT HEALTH. A MANUAL FOR DISTRICT VISITORS, NURSES, AND MOTHERS. By J. S. C. MACMILLAN, C.M.B., A.R., San. I. Pp. 128; 12 illustrations. London: Oxford University Press.

THIS manual is delightfully written, and may be read with profit by any lay or medical person interested in the betterment of the child. Its teachings and advice are mostly fundamental, but so clearly set forth as to impress them with force. The author considers in a brief way the necessary knowledge of anatomy; the simple things to know and care for in pregnancy; the keeping of both the mother and child well; the proper hygienic procedures for the baby.

The author is to be commended for not going too deeply into the subject of infant feeding in a book of this scope, especially when it is written essentially for the non-medical reader. A. G. M.

DIAGNOSTIC METHODS. By HERBERT THOMAS BROOKS, A.B., M.D., Professor of Pathology, University of Tennessee. Third edition; pp. 965. St. Louis: C. V. Mosby Company, 1916.

THIS is a very brief guide in history-taking, and the making of routine physical examinations and laboratory tests necessary for students in clinical pathology. The new third edition has an added chapter on the technic of staining and examination of smears, most important exudates, etc. The author advises, along with the use of his work, that the reader should study some extensive work on clinical diagnosis.

The book is similar to many others in the same field. It apparently serves a local purpose in the author's university, and can hardly appeal to the man outside of these medical halls. Some of the newer renal functional tests might have been added with profit to the reader. The type is clear; the paper is good; the binding is excellent—all that could be wished for in a well-constructed book. The directions are accurate, brief, and up to date; all features that make for a desirable laboratory guide. T. G. S.

THE PATHOLOGY AND TREATMENT OF THE SO-CALLED NERVOUS ASTHMA. By J. B. BERKART, M.D., Late Physician to the City of London Hospital for Diseases of the Chest; Corresponding Member of the Société Royale des Sciences Médicales et Naturelles de Bruxelles, of the Société de Médecine of Paris, etc. Pp. 54. London: Humphrey Milford, Oxford University Press, 1916.

BERKART in this small volume draws a sharp line of distinction between that form of paroxymal dyspnea in which the disturbing factor is "a transient obstacle in the bronchial tree" and that in which the air passages are perfectly pervious, speaking of the latter as "the so-called nervous asthma." The distinguishing feature of this type is the complete lack of physical evidence of any impediment to the ingress and egress of air during the attack. It generally follows, he believes, rickets which has affected chiefly the spine, only slightly the chest and lungs, and is based upon an endogenous neuropathy. His treatment is therefore directed primarily toward the neuropathic disposition, and his suggestions for the manage-

ment of such a condition are eminently logical and at the same time practical. He wisely taboos the widespread nasal treatment of these cases and believes the alleged anaphylaxis of eggs and milk has not been established on reliable grounds. T. G. M.

WOUND INFECTIONS. By COLONEL SIR ALMROCH E. WRIGHT, M.D., F.R.S., Consulting Physician to the Expeditionary Force. Pp. 96; 12 illustrations. New York: William Wood & Co.

THIS little work takes up the all-important question of how to handle wound infections, the data and experiments having their being in connection with the present war. Two chapters are devoted to the biological evolution of wound infections and the experimental investigation of white blood corpuscle emigration into wounds.

Treatment is outlined under three heads: (1) by antiseptics; (2) by physiological methods; (3) by vaccine methods.

In an epilogue the author makes a strong plea for a more systematic routine in the experimentation, treatment and publication of results of wound infections.

The book makes very instructive and interesting reading.

E. L. E.

INFANT FEEDING. By LAWRENCE T. ROYSTER, M.D., Attending Physician, Bonney Home for Girls; Physician-in-charge, King's Daughters Visiting-Nurse Clinic for Sick Babies, etc. Pp. 144; 3 illustrations; 2 charts. St. Louis: C. V. Mosby Company, 1916.

THE purpose of this book, as expressed by the author, is to furnish the essentials, and only the essentials of infant feeding in a compact and succinct form, for the busy practitioner. He realizes that the book contains many imperfections, but hopes that its purposes will be taken into consideration. He thus disarms criticism of its inadequateness as a text-book on infant feeding. The reviewer cannot refrain from the comment that the practitioner who is too busy to read more than a work like this on such an important and complicated subject as infant feeding, would do well to relinquish that part of his pediatric practice to those who can give it the time it deserves. J. C. G.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF CLINICAL MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO.

A Study of an Epidemic of Trichinosis with Cures by Serum Therapy.—B. F. SALZER (*Jour. Am. Med. Assn.*, 1916, lxvii, 579) makes a preliminary report of his clinical and experimental studies on trichinosis. Most of his findings are new and many of them are of such importance, if confirmed, that the author's summary of his findings is given practically in his own words. The Kernig reaction was present in all of fourteen human cases. The reflexes in the lower extremities were abolished in all the cases and are still absent (six months). Trichinæ were found in the blood in nine of the 14 cases and in the cerebrospinal fluid in 8 cases. These and other less important points have been demonstrated previously and are confirmed by the author. His newer clinical and experimental results are chiefly as follows: The diazo reaction was in direct proportion to the degree of eosinophlilia. The leukocytosis diminished as the eosinophilia increased. The blood coagulation time was markedly prolonged. In a child three months old trichinæ were still present in the cerebrospinal fluid three months after clinical recovery. In one case trichinæ were found in a pleural exudate and the disease was reproduced by injecting this fluid; they were not found in the urine of any of the fourteen patients. Trichinæ were not found in the uterus but they were abundant in the placenta. The embryos were present in large numbers in the milk of a nursing woman, and were also present in a piece of excised mammary gland. In one case complicated by furunculosis, trichinæ were found in the pus of a furuncle of the external auditory canal. On inoculation of the pus into a rabbit, trichinosis were produced. The feces were clay-colored throughout the disease in every case. This color, the author believes, is due to reduction of the bilirubin by living trichinæ, whose presence

in great numbers was demonstrated in one case by means of the duodenal tube. Trichinæ were present in the stools of all the cases throughout the disease. They were proved to be present by making the stools alkaline and allowing them to stand twelve to twenty-four hours. In experimental trichinosis, embryos were not found in the blood during the first five days. On the seventh day two or three were observed in every field. Trinchinæ were absent in the heart muscle. The use of serum from human patients who had recovered removed the eosinophilia persisting after recovery in man or animals within forty-eight hours. The injection of normal serum had no therapeutic value in man or animals, and the same was found true of salvarsanized serum and salt solution. In animals the injection of convalescent serum gives an almost complete prophylactic result. Animals fed with infected meat within twenty-four hours after the administration of the serum may develop a mild form of trichinosis. Animals fed at a period later than that prove to be immune. If immune serum is mixed with infected meat and then fed the animals do not develop trichinosis, although the injestion of the same meat without the serum is invariably followed by the disease. In 2 cases of trichinosis in the very active stage of the disease the use of immune serum proved to be of remarkable curative value. There was a decided drop in the temperature within six hours and the abnormal temperature was entirely gone within forty-eight hours. The eosinophilia showed a considereble drop within six hours; there was then a secondary rise and then a return to the figures found in normal blood within forty-eight hours. In twenty-four rabbits suffering from the disease experimentally produced the immune serum had a curative effect within twenty-four hours.

The Quantitative Determination of Amylase in Blood Serum and Urine as an Aid to Diagnosis.—P. Stocks (*Quart. Jour. Med.*, 1916, ix, 216) employed modifications of Wohlgemuth's method for determination of amylase and has made a special study of pancreatic disease to determine whether diagnostic aid might be secured by this means. He was lead to undertake the study because of the frequency with which cancer of the stomach and liver is found to be primary in the pancreas. The author gives in detail the technic of the method, together with observations on individuals with presumably normal amylase values. His application of the tests to patients with pancreatic and other diseases has led him to the following conclusions: Amylolytic ferment is present in the blood serum and urine of all healthy individuals, and has also been found in all the body fluids examined. The level is practically constant in the blood serum; the level in the urine is subject to diurnal variations due chiefly to the digestive functions. The ferment is of pancreatic origin and is absorbed directly by the blood. No proof of the action of anti-amylase has been found. Disease of the kidneys causing any diminished permeability of these organs reduces the amount of ferment in the urine, and consequently raises the amount in the blood. Any disturbance in the ratio D (blood): D and M (urine) indicates renal insufficiency. Severe passive congestion also raises the amount of amylase in the blood. With these exceptions, any increase of the ferment in the blood serum denotes pancreatic mischief. The values have been found raised in all cases of pancreatic

disease, the increase depending on the degree of obstruction in any part of the gland or its ducts, and on the acuteness of the condition. The highest values were found in a case of acute pancreatitis. The estimation of the amylolytic capacity of the blood serum and the urine is a most delicate test of the efficiency of the pancreas, and consequently is a most delicate and reliable test for disease of the pancreas, the author states. The use of the simplified modification of Wohlgemuth's method, and the use of an identical technic for serum and urine are justified, he believes, by the consistency and regularity of the results obtained.

Carbon-monoxide Poisoning. — Y. HENDERSON (*Jour. Am. Med. Assn.*, 1916, lxvii, 580) gives a resumé of his observations on carbon monoxide poisoning. Many of the facts he mentions are, as he says the discoveries of Haldane, whose work is not sufficiently well known to practitioners. The author's summary is as follows: Carbon monoxide is a physiologically inert gas, except in its affinity for hemoglobin. Its toxic effects are wholly due to the inability of the blood combined with carbon monoxide to transport oxygen to the tissues. A permanent compound with hemoglobin is, however, not formed. In the presence of excess of oxygen, or even of pure air, carbon monoxide is rapidly given off and the oxygen carrying power of the blood is restored. The continuance of coma, the subsequent tissue degenerations, and death after several days, resulting from carbon monoxide poisoning, are not due to retention of the gas, but are the results of injury to the brain and other organs by the insufficiency of oxygen supplied to them by the blood while the patient was breathing the gas. There is no reason to believe that either bleeding or transfusion of blood is beneficial. They are more likey to be harmful. Fresh air—with oxygen inhalation as early as possible (within one-half hour)—symptomatic treatment, and good nursing are the only measures to be recommended. Practically the die is cast for death, permanent defects, or complete recovery at the moment when the patient is brought out of the asphyxial atmosphere. It is just possible theoretically that alkali therapy may be beneficial in combating the acidosis induced by asphyxia.

The Treatment of Arthritis by the Intravenous Injection of Foreign Protein.—J. L. MILLER and F. B. LUSK (*Jour. Am. Med. Assn.*, 1916, lxvi, 1756) refer to the work of Kraus and of Lüdke, which showed that typhoid fever may be treated apparently as successfully with intravenous administration of colon bacillus vaccine as with typhoid vaccine. Lüdke later found that he could obtain similar results with a solution of proteose prepared by Drs. Jobling and Peterson. The authors then decided to apply this method of treatment to acute, subacute and chronic arthritides. As their supply of proteose was limited and as they believed the reaction was due solely to the foreign protein, they substituted a typhoid vaccine for the proteose. The bacilli from the Rawling's strain were killed by heating to 55° C. and were preserved by the addition of 0.5 per cent. phenol. In the preliminary cases a dose of 150,000,000 was given intravenously. "The reaction was the same as when the vaccine was given to a typhoid patient, except that the leukocytosis was much more marked, in two instanecs reaching

52,000. Immediately following the injection there was a moderate leukocytosis which increased slightly until the chill, which usually occurred in from five minutes to one hour. During or immediately following the chill, there was a rapid drop in the leukocytic curve resulting either in a normal count or a leukopenia, followed promptly by a rapidly developing leukocytosis, which reached its maximum usually at the end of four and occasionally at the end of twelve hours, gradually returning to normal in from twenty-four to forty-eight hours." Following the chill there was a profuse sweat lasting several hours. In three patients with acute arthritis there was a second chill which came on six to seven hours after the intravenous injection. A temperature of 105° was not unusual in the acute arthritides. Nausea and headache were practically always complained of after the chill. In three of ten cases of acute articular rheumatism, immediately following the intravenous injection of 150,000,000 killed typhoid bacilli, the fever terminated by crisis, the joint tenderness began to disappear, and within from twelve to twenty-four hours the joints were apparently normal. In these three cases the results were permanent. All of the seven remaining cases were very much benefited following a single injection, but the results were either not permanent or soreness remained in the affected joints. Three or four injections, however, sufficed to relieve all symptoms. Relapses nevertheless were frequent. The authors are now giving daily injections until four or five have been given in order to see if relapses can be avoided. Results quite as satisfactory were obtained in six cases of subacute arthritis of from three to nine months' duration. After three or four injections the patient could move his joints with comfort. Even better results were secured in cases of chronic gonorrheal arthritis of from two months' to three years' duration. All of seven cases showed decided benefit. The results appeared to be less satisfactory in two patients with acute gonorrheal arthritis. Complications in the joint cases such as endocarditis or pericarditis, seemed to be unaffected by the treatment. In gonorrheal arthritis, in fact, the urethral discharge was temporarily increased following the injection of vaccine. The treatment, the authors believe, deserves further trial. It is obvious that foci of infection, when found, should receive the usual treatment.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY AND ASSOCIATE IN SURGERY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL HOSPITAL AND ASSISTANT SURGEON TO THE UNIVERSITY HOSPITAL.

Localization and Extraction of Projectiles and Shell Fragments.—FLINT (*Ann. Surg.*, 1916, lxiv, 151), writing from his experience in a

French military hospital, says that there have been great differences of opinion expressed by military surgeons concerning the advisability of extracting or leaving projectiles or shell fragments either before or after they are healed in the tissues. He gives the following indications for extraction: (1) Instances where the projectile or fragment forms a focus of suppuration which will probably continue until either the fragment is removed or until it is discharged spontaneously from a fistula. (2) Instances where the foreign body is causing pain. This may be situated either in the muscles, near the bones or nerves, in tendons or even superficially. Not infrequently the pain may be due to the cicatrix surrounding the fragment rather than the fragment itself. (3) Instances where the wounds of entrance or exit have healed, leaving the projectile in the tissues surrounded by a small abscess or focus of infection encapsulated from the surrounding tissues. (4) Any interference with the function of the tissues or organs forms a rational indication for a removal of the offending foreign body. (5) Instances where the presence of the foreign body may influence the mental condition of a patient to a degree which justifies its removal. (6) Another group of cases which are of great importance in military surgery belong to the malingering type, who complain that shell fragments are painful in order to avoid the responsibility of further military service Such instances require removal in order to restore the wounded man to military service. (7) Cases where a lead projectile may give rise to lead poisoning. (8) When cases are brought in fresh from the front and operations are performed for infections, better drainage, removal of loose bone fragments in compound fractures, etc., the projectiles should be removed if possible. The contraindications may be briefly summarized as follows: (1) No operation should be performed which does more injury to the tissues than the presence of the foreign body. (2) The operations should not be performed in clean cases where there is not a reasonable expectation of aseptic healing or a great probability of finding the projectile. The methods for the localization of the foreign body must be suited to the requirements of the individual case. Radiography was not satisfactory. Up to the present time the vibrating magnet and the Sutton cannula with the harpoon are perhaps best adapted for immediate operation on cases fresh from the front, although their limitation must be constantly borne in mind. The profundometer of Irvin is by all odds the most useful and the most general in its application, and provides localization data upon which practically any extractor can be made.

Observations on the Diagnosis and Treatment of Trifacial Neuralgia.—Beckman (*Ann. Surg.*, 1916, lxiv, 242) studied 177 cases of trifacial neuralgia which came under his observation. A mistaken diagnosis is not often made by those who have seen a number of cases, A continuous aching pain or pain that throbs with the pulse is not trifacial neuralgia. The pain is very often started by the slightest irritation of a certain localized area on the face or tongue, and occasionally by the irritation of a single tooth, "doloro genetic zones" or "trigger zones." Beckman's cases have not appeared to be more neurotic than the average. An excision or evulsion of the peripheral nerve branches was done in 19 cases. The longest period of relief in

any of the series was two years. In this patient the infraorbital nerve was evulsed and a screw placed in the foramen. Only five of the patients were relieved for one year or longer. The average time of relief was 8.4 months. In 146 patients the method of Levy and Baudoin was employed for injecting the main nerve branches at the base of the skull with alcohol. Letters have been returned from 120. The plan has been followed by injecting the second and third divisions of the nerve when one of them was involved. Occasionally some bleeding resulted, which produced considerable tension underneath the temporal fascia. In three patients, there was inflammatory reaction of the cornea which cleared up within a few days; in two there was temporary paraysis of the external rectus muscle of the eye, and in six, stiffness of the muscles of mastication, which gradually subsided. The latter were patients who had had several injections. In one instance the relief lasted five and one-half years, in another three years, and still another three and one-half years. However, only 30 were relieved for one year or longer. The average length of time for the whole series of 120 from whom letters were received was 9.4 months, a slightly longer average than the time of relief following the series of operations on the peripheral branches. Relief of pain for six months or less occurred in 77 of the 120 (64 per cent.). Beckman has had no experience with injections into the Gasserian ganglion, and thinks that if this method becomes generally adopted there will be many serious complications. Eighteen patients have had operations on the Gasserian ganglion. Eleven patients had the ganglion removed after the Hartley-Krause method, 1 was operated on by the method of Abbe, and 6 by the method of Frazier. Thirteen of the living patients have been completely relieved of their pain or the recurrences have been so slight that they consider their condition satisfactory. The remaining 3 patients have had recurrences, probably from incomplete operations. There were two operative deaths in this series. Beckman believes that the same number of patients operated on today would give approximately 100 per cent. permanent relief from pain. At the present time evulsing the posterior nerve root or removing the ganglion entirely is the only operation insuring permanent relief, and the mortality is no higher than that of many serious operations performed daily by surgeons throughout the country. It should be the operation of choice for a person in reasonably good physical condition.

More Radical Treatment of Duodenal and Gastric Ulcer.—Deaver (*Ann. Surg.*, 1916, lxiv, 294) says that where the ulcer is small and is located upon the anterior wall of the first portion of the duodenum it is his practice to exercise it, close the opening in the intestine, plicate the duodenum and make a posterior gastro-enterostomy. When an ulcer in this portion of the intestine is large, but extends short of the head of the pancreas, he amputates the duodenum below the lesion, purse strings it, inverts, excises the pylorus, and makes a posterior gastro-enterostomy. When the ulcer is on the posterior wall of the first portion of the duodenum and not too adherent to the posterior abdominal wall to permit of freeing the duodenum, he practises the same technic as in large ulcers upon the anterior wall. In acute perforation of a duodenal ulcer he makes a posterior gastro-enterostomy

at the primary operation. He has now operated on 44 patients in this manner with but one death. He always treats the chronic indurated ulcer of the pylorus by doing a pylorectomy. When the induration of such an ulcer involves the lesser curvature in proximity to the pylorus, he does a subtotal gastrectomy. Posterior gastro-enterostomy does the greatest good when the pylorus is obstructed. In ulcers located other than at the pylorus does but little if any good. That this operation does any good by drainage alone, he thinks doubtful. It does most good when there is pyloric obstruction and when the ulcer is excised. When excision of the ulcer has not materially interfered with the mechanics of the stomach, with the exception of the pyloric ulcer, posterior gastro-enterostomy should not be done. To summarize, he has come to the conclusion that all ulcers of the duodenum or stomach are best treated by excision.

Observations on the Occurrence of Syphilis in the University of Michigan Obstetric and Gynecologic Clinic.—PETERSON (*Surg., Gynec. and Obst.*, 1916, xiii, 280) says that for the past year there has been a hospital rule that every in-patient should have a Wassermann taken, and the rule has been fairly well carried out. In 2000 patients there were 110 distinctly positive Wassermanns in which the diagnosis in almost every case was confirmed by the department of syphilology. Among the doubtful reactions there were 8 in which the patients were afterward proved to be syphilitic. This shows that 6 per cent. of the general run of hospital patients are syphilitic. Wassermann reactions should be taken routinely, especially where even careful histories fail to arouse suspicion of latent syphilis. The percentage of lues in 381 cases in the University Maternity was 4.7 as shown by the Wassermann reactions and expert physical examinations. In 18 cases of syphilis among the number examined only 8 gave a history of lues. In only the same number (8) were there positive physical signs of lues. As shown by the histories of the 18 cases there is a greater chance for the syphilitic mother treated by salvarsan and mercury to give birth to a living, full term child than where no treatment is given during pregnancy. The newborn infants of the mothers so treated do not give positive reactions, although undoubtedly they are syphilitic and later probably will show signs of the disease. A certain proportion of the newborn children of untreated syphilitic mothers will give positive Wassermanns. Out of 390 gynecologic patients subjected to the Wassermann test, 22, or 5.6 per cent., gave positive reactions. In only 5 of the 22 luetic patients was there a history of syphilis. Hence the importance of such examinations, or a serious general disease will be overlooked and the gynecologic patient will remain uncured.

The Transplantation of the Articular End of Bone Including the Epiphyseal Cartilage Line.—HAAS (*Surg., Gynec. and Obst.*, 1916, xxiii, 301) says that from his experiments and the results in general on transplanted bone the following conclusion is offered regarding the fate of bone after transplantation. Although each part of transplanted bone possesses the power to regenerate independently and without the aid of neighboring bone, this autonomous newly formed tissue does not possess that property which is necessary for a continued existence, and

it will ultimately entirely disappear. Some additional stimulus is needed and such conditions are only obtained when the transplant is in direct contact with normal growing bone. Therefore, when there is failure of such connection the transplanted bone at first shows evidence of regeneration but if a sufficient time is allowed to elapse, it will ultimately entirely disappear. However, if it is united with the cut surface of normal bone it will continue to live because certain necessary additional stimuli and new elements will be supplied by the host. It is possible that certain chemical or physiological stimuli are supplied by the living intact bone, after which the regenerated bone on account of these additional factors is able to persist permanently. Undoubtedly some definite osseous elements from the bone of the host invade the transplant and either replace the temporary bone or give to it certain requisites for its perpetuation. Although function may play a factor in the development of bone it is not of prime importance in determining the permanency of that tissue.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

PROFESSOR OF CLINICAL MEDICINE IN THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

Specific Treatment of Infantile Paralysis.—SOPHIAN (*Jour. Am. Med. Assn.*, 1916, lxvii, 426) writes concerning his experience regarding treatment in the present epidemic of infantile paralysis in New York City. He divides the treatment into: (1) relief of hydrocephalus; (2) intraspinal injection of serum; normal serum, horse serum or convalescent; (3) relief of special symptoms, as respiratory paralysis; (4) symptomatic general treatment, and (5) orthopedic treatment. Hydrocephalus with its pressure symptoms is most pronounced during the acute stage. In most cases it is only moderate, but not infrequently, especially in the cerebral cases, it is quite pronounced. In the latter the patients are often very stuporous, with twitchings, convulsions and respiratory embarrassment. Paralysis of the respiratory centre is the usual cause of death in infantile paralysis. Early relief of respiratory embarrassment is therefore important. One lumbar puncture usually suffices, but in some cases it must be done several times till relief is permanent. So far a highly immune serum for poliomyelitis has not been obtained. Sophian believes that the production of a hyperleukocytosis in the cerebrospinal fluid has a very distinct therapeutic value in the treatment of epidemic poliomyelitis. Such a hyperleukocytosis can be induced by intraspinal injections of normal horse serum or human serum. The objection to horse serum seems to be the sensitization to foreign protein; therefore, normal human serum would be preferable. In order to be of most value, the serum should be used

very early in the disease, during the acute inflammatory stage, if possible in the preparalytic stage, especially if prevention of paralysis and abortion of the disease is to be looked for. The use of a blood serum obtained from cases convalescent from poliomyelitis offers the advantage of a human serum plus the presence of immune bodies. That serum obtained from at least recently convalescent cases contains immune bodies has been proven by the neutralization test in the monkey. Netter reported the use of convalescent serum in thirty-two cases, with excellent results. With regard to the effects produced by the intraspinal injection of various forms of serum, Sophian states that in a series of cases treated by convalescent serum, the results were certainy no better than in those treated by normal horse serum. In the normal horse serum series, two cases treated in the preparalytic stage were aborted and one case was aborted under the convalescent serum treatment. The best results were obtained in early cases but some of the late cases treated showed more improvement than is generally seen in untreated cases. There was more rapid convalescence and improvement in the paralytic condition. Sophian has had very little experience with the local administration of epinephrin. Respiratory paralysis is the most common cause of death in infantile paralysis. It is therefore of prime importance to meet this complication early, so as to tide the patient over the critical period until congestion and inflammation about the respiratory centre subside. In comatose patients, the pharyngeal respiratory apparatus has been suggested by Meltzer and for conscious patients, if possible early after respiratory difficulty has set in, the administration of oxygen under pressure by the method of Meltzer may be of value. General treatment is very important as the patients are frequently helpless and require especial care as to feeding and care of bowels and bladder. Orthopedic treatment should be begun as early as possible after the acute symptoms subside.

The Treatment of Tuberculosis with Cyanocuprol.—OTANI (*Jour. Exper. Med.*, 1916, xxiv, 187) reports the results of treatment in eighteen cases of tuberculosis, in a numbr of which very favorable results were obtained, although in some absolute failure was noted. He believes that cyanocuprol is markedly effective in tuberculosis and that it will play an important part in clinical medicine. It may be used more generally than tuberculin. The amount of the dose is closely related to the reaction and the final results. It should be determined for each patient after a careful examination of his symptoms. The maximum dose of 8.5 c.c. should in no case be exceeded. The shortest interval between injections should be two weeks. If the drug is given after a shorter interval, no improvement is observed and the effects are sometimes dangerous. In order to obtain the best results the patient should be placed under conditions of complete physical and mental rest after the injection; this applies even to light cases. During the period of the treatment irritants to the lesion, such as potassium iodide or tuberculin, should be avoided; apricot juice, guaiacol and its derivatives and iodol are contraindicated. No marked idiosyncrasy has been noted and no accumulative effects have been observed.

Metabolism Studies Before and After Splenectomy in Case of a Pernicious Anemia.—PEPPER and AUSTIN (*Arch. Int. Med.*, 1916, xviii, 131) report metabolism studies in a case of pernicious anemia before and after a splenectomy which was performed for therapeutic effect. The patient was an adult with pernicious anemia of a moderately hemolytic type in whom the splenectomy was followed by the disappearance of the discoloration of the skin and by prompt and persistent improvements in the condition of the blood and general health. Metabolism studies before and after splenectomy gave the following results: A slight positive nitrogen balance before splenectomy was followed by an increased nitrogen retention fourteen days after operation and a return to the preoperative balance after one month. The output of uric acid, although never exceeding normal limits, showed a decrease of 22 per cent. after operation. The output of iron through the feces, although never above normal, showed a decrease of 40 per cent. after operation. The excretion of urobilinogen and urobilin in the feces before splenectomy was about three times the normal; two months after operation the output was about one-seventh of that before splenectomy.

Results Obtained in the Treatment of Diabetes Mellitus.—JOSLIN (*Bost. Med. and Surg. Jour.*, 1916, clxxv, 147) says that during the year ending May 1, 1915, 211 cases of diabetes came under his observation, and of this number 31, or 15 per cent., died; during the subsequent year 314 cases were seen and 37, or 11.7 per cent., have died. These figures represent a decrease in mortality over the previous year of about 20 per cent. Joslin says these figures are encouraging, but they become still more so when it is considered that a study of the 37 fatal cases seen this last year shows that death might have been deferred in about one-half of these if the methods of treatment now in general use had been adopted. The author states that in a study of the causes of death of 408 cases of his series, it was found that two out of every three (66 per cent.) died of coma, that 87 per cent. of all these who succumbed during the first year of the disease died of coma, and that this was the case in 100 per cent. of the fatal cases in children. Therefore, if the mortality of diabetes is to be reduced, our energies should be directed first toward the avoidance of coma, because the treatment of coma is so unsatisfactory; and second, particular attention should be exercised in the management of cases of diabetes in the first year following the disease. Furthermore, all cases should be persistently followed up, and the good effects of treatment not be allowed to lapse by indifference or neglect.

The Rate of Absorption of Various Digitalis Preparations from the Gastro-Intestinal Tract.—HASKELL, MCCANTS, and GARDNER (*Arch. Int. Med.*, 1916, xviii, 235) found that the infusion of digitalis seems to be absorbed more slowly than the tincture in animal experiments that they conducted. They also tested some of the special digitalis preparations which have been claimed to possess a more rapid rate of absorption from the gastro-intestinal tract than official digitalis preparations. The three special preparations of digitalis, namely, digipuratum, digalen, and digipoten, seem to possess no decided advantage over the official tincture. Their chief practical disadvantage is their high com-

parative cost. Digipuratum in their experiments seemed to be absorbed less rapidly than was the tincture. The sample of digipuratum tested was somewhat stronger than the official tincture, but this did not nearly compensate for the difference in absorption. Digalen was absorbed more rapidly but the variability in strength and the low standard of strength (only about one-fourth the physiological activity of the tincture), together with the relatively high cost of this preparation, more than offset this possible advantage.

The Treatment of Amebic Dysentery.—Bates (*Jour. Am. Med. Assn.*, 1916, lxvii, 345) says that one of the first and most necessary factors in treatment, whether the case is mild or severe, is complete rest. The patient is put to bed and given a saline purge or castor oil. He is kept in bed until all the acute symptoms have subsided. After the purgative has acted, emetin or ipecac is begun. Bates advises one-half grain injections of emetin daily for an adult until two grains are given. The dose is then increased to one grain a day and continued until all amebæ disappear from the stool. This will usually require a total of from five to six grains of emetin. At this time the emetin is discontinued and bismuth subnitrate in large doses is begun. Bismuth acts in two ways: (1) as a sedative on the intestinal tract and as an aid toward the healing of the ulcers present; (2) as was first pointed out by Deeks, bismuth itself acts as an amebicide and is an added help in destroying such amebæ as may be left or those that may be formed from the "encysted stage." Bismuth is usually given in one dram doses every four hours until the stools are well formed, and until some constipation is present. It may then be reduced to one dram, three times a day until the patient is discharged as well. Enemas of normal saline solution, 2 or 3 quarts at a time, are begun as soon as the effect of the salts or castor oil has subsided, and are used every four hours during the waking hours, and continued in this quantity throughout the entire period of the administration of ipecac or emetin. They may then be reduced to two or three a day and later to one a day, merely to prevent the constipation following the bismuth. Experience has shown that sweet milk is the best food in amebic dysentery. It may be given every two hours during the day in quantities of from 4 to 8 ounces at each feeding. After the more acute symptoms have passed and the stools are beginning to be formed, the milk may be gradually increased in amount and the intervals between feedings lengthened. Soft-boiled or poached eggs may be added to the diet with one slice of dry toast at each feeding. To carry out this treatment until one is reasonably sure that all ulcers are healed will require in the acute cases at least four weeks time and in the more severe cases from six to eight weeks. Bates is confident that the treatment just outlined will effect a cure of amebic dysentery in a large majority of cases. Nevertheless it must be expected, especially in the tropics, that some cases will be encountered so far advanced that no treatment can be of help. Occasionally relapses will occur in spite of the treatment outlined. In cases when two or three efforts at treatment by medicinal means have failed, appendicostomy will have to be advised. After this the colon should be flushed out several times a day with saline solution, followed by powdered ipecac suspended in some bland material, such as mucilage acacia.

Dietary Deficiency as the Etiological Factor in Pellagra.—VEDDER (*Arch. Int. Med.*, 1916, xviii, 137) in his conclusions states that there is a certain similarity between pellagra and other known deficiency diseases, namely, beriberi and scurvy. Much of the evidence that has been presented as a proof of the infectious nature of pellagra can be reasonably explained in accordance with a deficiency hypothesis. A deficiency is demonstrable in the diets of most pellagrins. This deficiency appears to result from the too exclusive use of wheat flour, in association with cornmeal, salt meats and canned goods, foods that are known to be deficient in vitamins. Changes in the diet of the people of the South have occurred during the past ten or fifteen years. Since all the changes that have occurred are not known and they cannot judge accurately the importance of the known changes, it is unscientific to assume that the recent increase in pellagra cannot be due to such changes. The hypothesis that pellagra is caused by a deficiency is very plausible and must be taken into consideration in subsequent studies of this disease.

Hay Fever. Its Treatment with Autogenous Vaccines and Pollen Extract.—MEDALIA (*Bost. Med. and Surg. Jour.*, 1916, clxxv, 201) says that the bacteria found in the secretions of the nose and eyes of hay fever patients previous to their attacks and during their supposedly healthy condition are markedly suggestive of the important role played by such bacteria and their products. They are, he believes, the determining factor between individuals being susceptible to hay fever or not, since they may be, in a measure, responsible for the breaking up of the pollen, setting free the albumens and thus causing pollenosis. The bacterial infection, though secondary to pollenosis, is apparently responsible for the difference between pollenosis, producing a mere transient sneezing, or true hay fever attacks with all their accompanying symptoms. The good results obtained by the use of autogenous vaccines, as reported in the literature and his personal results, suggest to the author the important relation of bacteria to this disease. He reports six cases treated with a combination of autogenous vaccines and pollen extracts, all resulting in "seasonal cures." The results in these cases have been so decidedly beneficial that he believes the conclusion is justified—that the autogenous vaccine has yielded better results in the treatment of these hay fever patients than any other therapeutic procedure thus far suggested in the treatment of this disease.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND FREDERICK O. WAAGÉ, M.D.,
OF PHILADELPHIA.

Care and Feeding during the First Month.—PISEK (*Arch. Pediat.*, 1916, xxxiii, No. 6) states that in spite of marked decrease in the infantile

mortality, that of the first month of life is still woefully too high, and can be lowered only by active measures of prevention and correction. In spite of the well-known fact that babies thrive so much better on breast than on cow's milk, and that 85 per cent. of all infantile deaths are among those artificially fed, many are still removed from the mother's breast for insufficient reasons by the physician or nurse. Their decision is often based on the fact that no milk has appeared in forty-eight or seventy-two hours, or upon one hasty or inaccurate examination of the milk, or because of vomiting or an occasional abnormal stool. Every effort should be made to enable the baby to have the breast alone, or at least part breast feeding during this first month of life, for, while it will apparently do well for ten days or two weeks on a formula, its resistance then breaks down and its digestion becomes sadly disturbed and is hard to correct. Even a small amount of breast milk aids in the digestion of the cow's milk. If artificial food must also be supplied it should be a weak formula, low in fats and proteins, although high in sugar. An amount of food necessary to produce a gain in weight need not be given, or, in other words, the caloric requirements are not to be fulfilled until the end of the second week is reached. The three-hour interval is preferable, for, although the newborn infant can be trained to take the breast at four-hour intervals, it is not a natural interval, and unless vigorous, he is apt to need, in addition, artificial food. Weighing before and after a nursing throughout at least one whole day is essential in questionable cases to determine just how many ounces he is receiving. The author's experiments with the Roentgen-rays on infants' stomachs proved conclusively that babies can take an amount far in excess of their rated gastric capacity, because the milk tended to pass at once into the duodenum.

Acute Poliomyelitis: The Clinical Types of the Disease.—Koplik (*Arch. Pediat.*, 1916, xxxiii, No. 8) says that poliomyelitis is primarily an epidemic disease, and as a sporadic condition has attracted very little notice. The sporadic cases do not differ clinically from the epidemic type of the disease. An attempt to connect this disease with the occurrence of cases of cerebrospinal meningitis, has broken down to give place to the feeling that poliomyelitis is an entity, clinically occurring in epidemics in the late spring to late autumn. We owe much of our clinical knowledge of the disease to Media, who described the clinical types of acute epidemic poliomyelitis in 1884, much to the astonishment of most pediastrists, who still retained the simple picture as portrayed in older text-books of poliomyelitis anterior, as a simple infantile paralysis. This old conception of poliomyelitis, which without prodromata, was followed by an overnight paralysis of one or more extremities, has been lost sight of in the more thorough modern clinical analysis of the symptomatology of the disease, and we can now describe the following types: (1) The abortive; (2) the bulbospinal; (3) the cerebral and meningeal; (4) the bulbopontine. These types may be easily understood if we conceive poliomyelitis to be an acute infectious disease, and to the extent to which the infection goes, to that extent do we obtain a symptomatology, so that the old descriptions of the disease as an involvement of the ganglion cells of the anterior bones of the spinal cord must today be looked on as a small fractional part of the

story. The abortive is probably from a scientific epidemiological standpoint the most important type of the disease, for it is through these cases that the disease is spread to others. It is the type which does not go into paralysis, and with recovery leaves the patient uninjured as to the muscular motor apparatus. In an epidemic, fever, headache, vomiting, slight rigidity of the neck, increased or diminished reflexes at the knee must be carefully observed for further development. Aside from an epidemic few would give such symptoms a place other than among the extremely indefinite signs of an affection. The meningitic and cerebral types should be combined, because of the cerebral symptoms which give rise to a picture closely simulating meningitis. The meningeal form runs its course with cerebral symptoms due to a real injection of the meninges of the brain and cord. The bulbar or pontine type of the disease is another form which has only been recognized lately and deserves notice as a distinct form of poliomyelitis.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Acidosis Complicating Pregnancy.—ELY and LINDEMAN (*Am. Jour. Obst.*, July, 1916) report the case of a multipara who in her first pregnancy had great disturbance of digestion without definite symptoms of nephritis, but with acetone and diacetic acid in the urine. Labor was normal, but the child suffered from vomiting and disturbance of digestion. During the second pregnancy acetone and diacetic acid were present at the second month, and vomiting occurred. Rapid loss of weight followed. Use of alkalis and irrigation of the colon produced no effect. Rectal feeding did little good. Pulse and temperature continued normal, but the patient became profoundly toxemic. In the thirteenth week of pregnancy the uterus was emptied. This had no effect upon the vomiting. Analyses of the blood were then made, and direct transfusion was practised, taking the blood of the husband of the patient. This was done after the blood of twelve other persons had been examined to find one most suitable. For twenty-four hours before transfusion the donor was given large doses of bicarbonate of sodium; the effect upon the patient was surprising. At 12.30 P.M. 400 c.c. of blood was taken from the patient and 1100 c.c. transfused from the donor, with 300 c.c. of Lock's solution. Beginning two hours after transfusion the patient was given predigested food every two hours, with soda solution in the bowel every four hours. The patient vomited but three times in the next twenty-four hours, and after that was able to take diet and preparation of iron. A second transfusion from the same donor was given, using a smaller quantity, and the patient went on to uninterrupted recovery. Before the transfusion

the percentage of urea in the blood was low, and this increased decidedly after the transfusion. Blood ammonia was undoubtedly high before transfusion, for three days after it was more than twice the normal. It is interesting to note that the carbon dioxide of the blood plasma was 55 per cent. before transfusion, and that after transfusion this rose to 94 per cent. This valuable report should draw attention to the importance of acidosis in the toxemia of pregnancy. It will be observed that there was no evidence of kidney involvement, that emptying the uterus did no good, and that the only efficient measure consisted in correcting the condition of the blood. Transfusion by the syringe method is comparatively simple and safe. If the possibilities of acidosis should be kept in mind in all cases of toxemia, a prompt diagnosis and efficient treatment after the method employed by these writers should be tried.

Labor following Ventral Suspension.—CALDWELL (*Am. Jour. Obst.*, July, 1916) reports three cases of labor complicated by ventral suspension in which serious conditions developed. The first patient was a multipara who had a curetting, repair of the perineum, and ventral suspension of the uterus. The following pregnancy had preceded normally, but at its close it was found that the fetus was in transverse position and that this could not be corrected by external manipulation. The patient was admitted to Bellevue Hospital with slight pain. On examination the cervix was high, and pointing directly backward and toward the promontory. It was partially softened and admitted two fingers. No presenting part could be made out. Six hours after admission the membranes ruptured, the uterus was in tonic contraction with a beginning retraction ring. The cervix was high, pointing directly backward toward the promontory, and there was dilatation for three fingers. Under anesthesia the head and a foot were found in the lower segment, and a slow podalic version was done; the cord did not pulsate but the patient was allowed to come out of the anesthesia. A tight binder was applied with the hope that the patient would deliver the fetus in breech presentation. Very slight traction was maintained on the child's foot. Although the cervix completely dilated, and pains were good, there was no advance. The patient was again anesthetized and slow breech extraction performed; the aftercoming head was perforated and delivered. Following the birth of the child there was copious bleeding, and the patient became severely shocked. On removing the placenta by the hand a tear of the cervix on the right side was discovered. A hot intra-uterine douche was given and the cervix and vagina firmly packed, and the patient stimulated, but death occurred in less than two hours without further bleeding. At autopsy very dense fibrous adhesions were found between the anterior surface of the uterus and the abdominal wall. On the right side a tear extended obliquely upward for 12 cm. with bleeding into the right broad ligament. A well-marked retraction ring was still present. The second case was a primipara who had previously an operation removing the right ovary and appendix. A year after she had a second operation for adhesions. A third operation was done to free adhesions. She was admitted to hospital thirty-two weeks pregnant, with the history of almost constant abdominal pain. The abdomen was rigid and tender. The stomach

was distended but the intestines were not. The uterus was contracted and adherent to the abdominal wall. The cervix was high above the promontory, directed backward; the external os admitted one finger; the internal was closed; there was a slight discharge; the membranes unruptured. The patient was given morphin, but after fourteen hours the cervix did not dilate and section was performed. On opening the abdomen the adhesions were so dense that an opening was made into the sigmoid; injuries to the intestine were immediately repaired. A dead male child was delivered by section, followed by hysterectomy. The operation was followed by persistent vomiting and distention, with death forty hours after. The third case was a multipara admitted to hospital previously with premature separation of the placenta treated by section, followed by complete recovery. She was next admitted to the hospital in the thirtieth week of her pregnancy, with sharp pain in the abdomen followed by vomiting. The abdomen was relaxed and a seven months' fetus could be felt apparently directly underneath the skin; the cervix was hard and did not dilate. There was bleeding at intervals with foul discharge. On section a sac was found in the abdomen containing a dead macerated fetus in foul-smelling pus and gas. The sac was adherent, gangrenous, and removed with great difficulty. Death followed operation. These interesting cases give added testimony against the operation of ventrosuspension in all women during the child-bearing period. When this condition is complicated by pregnancy delivery by section is invariably the safest procedure. The second point of interest is the difficulties caused by extensive adhesions. The reviewer's experience has led him to consider extensive adhesions complicating pregnancy as one of the most difficult and dangerous complications. In one patient a successful Cesarean section was followed some years later by a second operation for the removal of an ovarian tumor complicating the second pregnancy. This proceeded smoothly; the operation was done in early pregnancy because the tumor had become wedged in the pelvis and its pedicle twisted. A smooth recovery followed this, and a second delivery by abdominal Cesarean section was performed later on. At this last operation extensive adhesions between the remains of the right broad ligament, whence had been taken the tumor, and the uterus were present. The emptying of the uterus caused traction on these adhesions and ruptured a large vein in the right broad ligament. The hemorrhage was alarming, but immediately repaired. During the next few days obstruction of the bowels developed, caused by adhesions between the bowels and the torn broad ligament, and although the abdomen was reopened, the patient did not survive. In a second case who had had a Cesarean section, a second section was necessary, and hysterectomy was requested. Adhesions were so extensive that in closing the broad ligaments and stump, the ureters were occluded by pressure. This was subsequently discovered by catheterizing the ureters; the abdomen reopened; the obstruction removed, and the patient making a complete recovery.

Two Cases of Weak Uterine Scars following Cesarean Section.—Beck (*Am. Jour. Obst.*, July, 1916) reports the case of a patient, aged twenty-seven years, who had been delivered two years previously by

Cesarean section. After twenty-four hours' labor the patient was sent to hospital by a midwife. She was delivered by Cesarean section but had fever during the puerperal period; the woman became infected and opened down to the peritoneum. Six weeks later the patient returned to the clinic with a hernia at the site of the abdominal incision. When pregnancy subsequently developed there was a thinned-out scar on the anterior wall of the uterus through which the fetal parts could be very easily outlined. The patient was within ten days of term, and it was thought best to have her enter the hospital. A second section was performed and the anterior surface of the uterus and omentum were densely adherent to the abdominal wall, and the uterine scar was very much thinned. The uterus was opened through these adhesions, making the operation extraperitoneal. Mother made an uninterrupted recovery and the child was in good condition. The second patient was also aged twenty-seven years, and in a previous pregnancy had eclampsia. At this time she was delivered by Cesarean section, mother and child leaving the hospital on the twenty-fifth day. At the end of the second pregnancy she returned to the hospital in labor, the fetus lying obliquely with the breech in the left iliac fossa and the head in the right upper portion. The cervix was almost dilated and membranes unruptured. Under anesthesia it was impossible to move the head, which was bulging through the thinned-out scar of the previous section. The membranes were ruptured, a foot was brought down, and the child delivered by breech extraction. During the delivery the lateral mobility of the head was restricted until the breech had descended far enough to allow the head to be pushed out of the bulging portion of the uterus.

The Puerperal Period Complicated by Sarcoma of the Ovary.—Brodhead (*Am. Jour. Obst.*, July, 1916) reports the case of a negress, eighteen years old, who came to the hospital when pregnant and had a normal delivery with living child. The third day after delivery the temperature rose to 102.5° with rapid pulse, and the patient complained of pain and tenderness, with rigidity in the right inguinal and lumbar regions and in the epigastric and upper umbilical region. The leukocytes were 17,000. On the next day the fever was higher, the tenderness and rigidity increased, and on vaginal examination tenderness was found. Eight days after delivery a mass could be palpated in the right lower quadrant, tender, elastic, and movable, and a diagnosis of abdominal tumor was made. The blood count showed 21,000 leukocytes. On section a sarcoma of the right ovary was found and readily removed, the patient making a good recovery.

The Care of the Perineum after Labor.—Plass (*Johns Hopkins Hosp. Bull.*, 1916) compared the results in two groups of cases. In one the usual routine of antiseptic cleansing was employed. In the other the patient herself used tap water and soap and a wash cloth. In both groups the morbidity was practically the same. In another series of cases in which there had been laceration, and stitches had been taken, better results were obtained without antiseptic irrigation. The wounds healed more satisfactorily and there was a smaller percentage of infection and other complications.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Escape of Foreign Bodies into the Perineal Cavity through the Uterus in Attempted Criminal Abortion.—Two interesting cases of this character, both of which recovered after operation, are reported by BECKMAN (*Ann. de gynéc. et d'obst.*, 1916, xlii, 206). The first patient was a young woman, aged twenty-seven years, who had had two previous full-term pregnancies. Having gone somewhat overtime she went to a midwife, who introduced a laminaria tent. Subsequent to this she began to have abdominal pains, followed in a few days by increasing hemorrhage. On admission to the hospital her general condition was good, the abdomen soft, but she was bleeding freely. On examination a silk thread was found issuing from the cervix; this was easily pulled out, but did not bring the tent with it. The cervix was then dilated and the uterus curetted, without finding any foreign body or evidence of perforation. The next day signs of peritonitis became manifest, and the abdomen was opened under general anesthesia. Immediately a large quantity of malodorous pus escaped; the laminaria was found lying among the coils of intestine, which latter were dilated, congested, and in places covered with exudate. There was a quantity of pus and blood in Douglas's pouch. The uterus and adnexa were removed, the vaginal mucosa sutured to the peritoneum, and a gauze drain passed from the pelvis through the vagina, with a second drain through the lower angle of the abdominal incision. After a somewhat stormy convalescence the patient recovered. On examination of the extirpated uterus a perforation large enough to admit a lead pencil was found on the anterior surface just above the peritoneal reflection. The second case was a woman, aged thirty-six years, who had passed through eight normal pregnancies. Her menses failing to appear at the termination of her last lactation she feared another pregnancy, and introduced a bougie 30 cm. in length into her uterus. This was accomplished by placing one knee on a bed beside which she was standing; with one hand she then located the cervix, and with the other introduced the instrument as far as possible, when suddenly it escaped from her grasp and disappeared. She remained quiet the rest of that day, but the next morning began to have pains, and on the fourth day presented herself at the hospital. At this time the abdomen was tender, uterus small, cervix closed, and on examination a foreign body, evidently the bougie, could be felt in the anterior cul-de-sac. Immediate laparotomy disclosed the bougie covered by inflammatory omentum; the intestines were inflamed and lightly adherent. The point of perforation of the uterus was found near the right cornu. The uterus was removed without the adnexa; a drain was placed in the vagina and another in the abdominal wound. Save for slight fever the first few days the con-

valescence was normal. On examination, no trace of pregnancy was found in the uterus. Beckman thinks that in all cases of this character operation should be performed as soon as the diagnosis is made, and usually by the abdominal route, so that any intestinal injuries may be attended to. He does not think it necessary always to remove the uterus unless this is obviously infected and endangering the patient's life. In other cases, removal of the foreign body and simple suture of the uterine perforation may be entirely sufficient. If the foreign body is encysted in Douglas's pouch posterior colpotomy may be employed in place of laparotomy, the uterus in such cases usually being preserved, though if it is necessary to remove it this may be done by the vaginal route.

Syphilis in its Relation to Gynecology.—The symposium upon this subject which formed an important part of the program of the last meeting of the American Gynecological Society has apparently directed the attention of gynecologists to this heretofore much neglected subject to a very considerable extent. One of the comprehensive papers at this symposium, dealing with the pathologic changes produced by syphilis in the female generative organs, was considered in this department a few months ago. A brief report on the clinical frequency and importance of syphilis as observed in the gynecologic and obstetric services of the University of Michigan was presented by PETERSON (*Surg., Gynec. and Obst.*, 1916, xxiii, 280). The Wassermann test was made upon 390 gynecologic patients, and of these 22 gave sufficiently positive reactions to be judged luetic, amounting to about $5\frac{1}{2}$ per cent. of the total amount examined. While this is possibly a rather low average in comparison to that found in other hospitals over the country, the value of the routine examinations is shown by the fact that only 5 of the 22 positive cases gave a definite history of syphilis, with one additional suggestive history. In Peterson's opinion, the value of these tests cannot be overestimated, since if they are not employed, local conditions may be treated surgically or by other local methods, while the far more important general disease is overlooked. It is undoubtedly true that the diagnosis of syphilis from physical findings alone is far more difficult in women than in men, because the local manifestation are much less marked. Many of the cases that in the past have been puzzles to gynecologists because of their failure to yield to local or surgical measures have undoubtedly been of this type, and will clear up when the true nature of the condition is realized and appropriate therapy instituted. A condition which in the past has been almost completely ignored by gynecologists and obstetricians, which may at times constitute an important element in the symptom-complex presented by their patients, namely *syphilitic fever*, was considered by TAUSSIG (*Surg., Gynec. and Obst.*, 1916, xxiii, 274). He divides this into that occurring as secondary, late secondary, and tertiary syphilitic fever. The secondary precedes or is coincident with the outbreak of the rash. This is believed to occur in about 20 per cent. of all syphilitics, but the rise is not over 1 or 2 degrees and the duration three or four days, so that it often escapes notice. Occasionally, however, the fever is quite high and persistent. Late secondary syphilitic fever is less frequent and more difficult of diagnosis; Taussig

reports having seen two cases of this type, both occurring postpartum. In both these women there was persistent high temperature which could not be satisfactorily accounted for, but which disappeared promptly upon the institution of specific treatment. Both patients gave evidences of a syphilitic infection. Tertiary syphilitic fever is still less frequent in occurrence, but is of greater diagnostic importance, since evidences of lues are generally absent and the symptoms may have been forgotten by the patient. The fever is usually continuous, and is attended with an elevation of temperature to 102° or 103°. The cases of this condition of interest to the gynecologist may be subdivided into those in which tertiary syphilis of the genital tract caused the fever, and those in which a gynecologic or obstetric condition was complicated by syphilis in other organs producing fever. Of the former, Taussig has encountered only one definite case, since the gummatous lesions occurring about the external genitals of women and in the rectum apparently do not give rise to this fever. It is the deep-seated lesions, such as those in the liver and osseous system that more often produce it. In several cases of uterine syphilis with extensive gummatous infiltration of the parametrium, however, there was a temperature that could hardly be explained except on the basis of the syphilis, so that the author would class these as suspicious cases of tertiary syphilitic fever. Two instances of the second type are cited; in one of these the lesion was apparently in the liver and spleen, and the other in the bones. In the former salvarsan was given with sudden and complete cessation of the fever and disappearance of the enlargement of the liver and spleen which had been present; in the latter a hysterectomy had been performed, with a secondary laparotomy in an attempt to clear up the cause of the persistent temperature, when the occurrence of pains in the limbs suggested a syphilitic periostitis. Antiluetic treatment resulted in immediate cessation of fever, a gain of eighteen pounds in weight, and disappearance of the bone symptoms.

Regurgitant Menstruation through the Fallopian Tubes.—A rather remarkable example of this condition is reported by CHILD (*Am. Jour. Obst.*, 1916, lxxiv, 484). The patient was twenty-nine years of age, and had been married for three months. The history, obtained only subsequent to operation, was that in order to prevent conception she had had an "antipregnancy button" inserted in the cervix by a physician, who had instructed her to return to him each month just before the onset of menstruation to have the button removed. This precaution, however, she had neglected, and the button was worn through three periods, during which the flow was scanty, and was accompanied with severe pain, such as she had never had before. The pain became worse and finally continuous, and the button was then removed, but without relief. On examination the pelvis was tender, with fulness in the cul-de-sac. A posterior colpotomy revealed free blood in the peritoneal cavity; upon opening the abdomen the uterus was found to be normal, but the pelvis contained a large amount of thick, dark blood with a few soft clots. Both tubes were normal except for a slight enlargement; their distal ends when drawn up out of the exudate were found to be perfectly free, and the fimbriæ not adherent. From the lumen of both tubes the same dark, sticky blood as filled the

pelvis could be squeezed. The canal in each tube seemed to be very much larger than normal, however, as it was possible to introduce a large filiform bougie. The material found in the pelvis was of the same general appearance as that usually met with in cases of retained menstruation due to atresia of the vagina. It showed no tendency to adhere to the peritoneum or viscera, but could be sponged away perfectly clean. Careful search failed to show any traces of a small ruptured ectopic, nor did the character of the hemorrhage suggest this condition. The uterus was not distended, but this could easily be accounted for by the fact that the button had been removed for some time, and if it had been distended, it had had time to return to normal size. After removal of the exudate the patient made an uneventful convalescence; the pain was entirely relieved, and menstruation has since been normal.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

JOHN F. ANDERSON, M.D.,

FORMERLY DIRECTOR OF THE HYGIENIC LABORATORY, PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

An Outbreak of Anthrax Conveyed by Infected Shaving Brushes.—R. R. ELWORTHY, (*Lancet*, January 1, 1916) reports three cases of anthrax were definitely proved to be caused by infected shaving brushes. Of these, two, the D case and the B case, survived the disease while one, the W—P— case was fatal. Clinically, the W—P— case was an example of so-called erysipeloid anthrax, which is characterized by the insignificance or deferred appearance of pustules, rapidly spreading edema and a high mortality. It is usually seen in the neck or eyelids where the tissue is loose and cellular. Having proved the identity of the bacillus by culture and inoculation, an attempt was made to decide how the infection came about. The man's occupation in no way suggested anthrax. At the postmortem examination it was noted that the original area of infection came within the individual's shaving area. This suggested the idea that a new shaving brush might have been the cause of the infection after a small wound had been made by the razor edge. It was found that the man had been using a new razor for about a fortnight. This brush was obtained for examination and was found to be of poor quality, made of animal fiber, pig bristles horse-hair and cows' tails with a small amount of vegetable fiber. The brush was "lathered" with 20 to 30 c.c. of sterile broth made alkaline to phenolphthalein with 5 per cent. sodium hydrate. The washings were heated at 80° C. for fifteen minutes, centrifuged and the deposit

collected in broth and distributed through three agar plates. Colonies which proved to be B. anthracis on subculture and inoculation grew. Some of the deposit was injected into a rabbit which died in three days from typical anthrax, and when this rabbit's blood was inoculated into a guinea-pig the latter died. In order to meet the objection that the infection of the brush was due to contact with an abraded anthrax lesion, unused brushes were examined, and out of the nine examined eight showed infection by B. anthracis on inoculation into guinea-pigs and six showed colonies of this organism on agar plates. A brush from the same manufacturer which had been used in the D case by a man who had contracted facial anthrax, was examined, but it was found that it had been thoroughly cleansed after use, which had probably removed the spores. However, when the ends of the hair, set inside the handle, were examined, they were proved to be infected by inoculating an animal with washings from them. The animal inoculated died in eight days from anthrax. Samples of the so-called "goat-hair" and hog-bristles which were used in the manufacture of these brushes were obtained. Nothing was found in the hog-bristles, but plates made from the washings of the goat-hairs were covered with colonies, half of which were anthrax. The animals inoculated with these washings died in thirty-nine hours from a mixed infection, cultures from the blood and spleen giving a few anthrax colonies. In an attempt to find the source of the hair infection, 30 pediculi found in a guinea-pig dead of anthrax were planted on the surface of an agar plate and 2 gave rise to colonies of anthrax. The last 2 brushes examined were associated with the B case, in which the patient was a youth, aged twenty-one years, who developed a malignant pustule on the back of the neck. A guinea-pig injected with the washings from the brush, died on the sixth day from anthrax. Since the lesion was on the back of the neck, it was thought that the infection was carried by the fingers or face-cloth. Another case of anthrax due to infection by a shaving brush is reported by E. H. Snell and E. W. G. Masterman in the *Lancet*, January 29, 1916. The clinical symptoms were characteristic of anthrax infection and smears of blood from around the pustule which developed showed anthrax bacilli as did smears from the spleen-pulp. No connection between the disease and his occupation or home-surroundings could be found. As the deceased had recently purchased a new shaving brush, it was thought that this might be the source of the infection. An examination was, therefore, made of the brush and anthrax spores found in it. Some of the brushes of the same make were purchased, and out of these, two were found to contain virulent anthrax spores.

The Physical Chemistry of Disinfection.—Norton and Hsu (*Jour. Infect. Dis.*, 1916, p. 180) in the first of a series of articles on the mechanism of disinfection studied from a physicochemical standpoint, record studies on the action of the hydrogen ion obtained from formic acid and the effect of neutral salts and of sodium formate on the rate of disinfection of B. typhosus by the hydrogen ion. This rate is shown to be proportional to the hydrogen ion, and is greatly increased by the presence of salts such as sodium chloride and sodium nitrate, but is decreased on the addition of sodium or ammonium formate to the acid. This latter action is due to the change in ionization pro-

duced, as shown by the fact that when isohydric mixtures of formate and acid are used, the rate of disinfection is increased in the same manner as with neutral salts. The conclusions from this study are that hydrogen ions are intimately concerned in acid disinfection, that salts act as catalyzers to increase the rate of action except where the salt and acid have a common anion, in which case there is a resultant effect due to the positive catalysis of the anion and the negative catalysis of the undissociated acid molecules.

Responsibility for Typhoid Fever.—In the case of Vennen vs. New Dells Lumber Company (*Public Health Reports*, vol. xxxi, No. 6, February 11, 1916) 154 N. W. Rep. 640 (October 26, 1915), the Supreme Court of Wisconsin decided that the death of an employee caused by typhoid fever which was contracted by drinking impure water furnished by the employer was the result of an "accident" under the terms of the Workmen's Compensation Law, and that the employer was liable.

Preventives of Typhoid Fever.—Methods for the Destruction of Body Lice.—GALEWSKY (*Deutsch. med. Wchnschr.*, May 27, 1915) gives an account of certain experiments for the destruction of lice found on the persons of Russian prisoners, and describes in some detail the measures adopted to stamp out typhus fever among such prisoners. In order that large bodies of troops might be quickly handled, large factories, such as sugar factories, were converted into stations for disinfecting soldiers and their clothing—some of these buildings being large enough to cope with from 12,000 to 15,000 prisoners and their clothing every day. The prisoners are first thoroughly washed with soap and water, while their clothing is being disinfected by steaming, with the exception of leather articles, which are subjected to dry heat. Galewsky made experiments to determine the most satisfactory method for the destruction of lice in buildings occupied by Russian prisoners nearly all of whom were infected by insects. All the cracks and corners were first washed with a 3 per cent. solution of cresol soap and were then plastered up. The clothing was hung loosely on lines in the building, with the exception of a bundle of shirts, which, for experimental purposes, was tied into a firm bundle. 25 kilos of sulphur were burned in the building, special sulphur stoves being used for the purpose. After three hours, the doors and windows were opened, and two hours later the building was occupied by the prisoners, who in the meantime had been bathed. It was found that the lice and eggs were completely destroyed except inside the parcel of shirts. Further experiments by Schlesinger showed that lice and their eggs were killed in two hours by sulphur dioxid vapors, but that it took two and a half hours or more for formaldehyde vapors to effect the same purpose. Dry heat was found to be effective in the destruction of lice and their eggs in one and a half hours, provided the articles to be disinfected were not closely packed. The general conclusion was that sulphur dioxid vapor is the cheapest and simplest, as well as the most reliable for the destruction of lice and their eggs in fomites and buildings.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

JOHN McCRAE, M.D., M.R.C.P.,

LECTURER ON PATHOLOGY AND CLINICAL MEDICINE, MC GILL UNIVERSITY, MONTREAL
SOME TIME PROFESSOR OF PATHOLOGY IN THE UNIVERSITY OF VERMONT, BURLINGTON, VERMONT; SENIOR ASSISTANT PHYSICIAN, ROYAL VICTORIA HOSPITAL, MONTREAL,

AND

OSKAR KLOTZ, M.D., C.M.,

PROFESSOR OF PATHOLOGY AND BACTERIOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

The Etiology and Experimental Production of Herpes Zoster.—In a series of recent publications Rosenow and his co-workers have attempted to establish a principle in bacterial infections, guiding the localization of microörganisms to particular organs or tissues. This process they speak of as the "elective localization" of bacteria. The intention of the authors is to prove the inherent quality possessed by bacteria for definite tissues. During all of the researches carried out by this group of workers no interest is displayed in the exact nature of the bacteria under discussion and there is an entire disregard of the part played by tissues in their antagonism or susceptibility to infection. For the bacteriologist it is difficult to follow the mental gymnastics of these workers, which permits them to draw sweeping conclusions from the assumptions which constitute the basis of the theory as well as from the garbled inconstant results of their animal experiments. The senior author appears to be familiar mainly with the tonsils and teeth as atria of infection of man's common ills. In these locations he claims to have shown the presence of infecting agents which, depending upon the object of the study immediately in hand, were the cause of appendicitis, cholecystitis, myositis, gastric ulcer, erythema nodosum, and, lastly, herpes zoster. In this study ROSENOW and OFTEDAL (*Jour. Infect. Dis.*, 1916, xviii, 475) follow the same unscientific methods as have marked the previous investigations. The microörganisms obtained from the assumed atrium of infection are not determined as to their character by any of the known and accepted bacteriological methods. In some cases it is stated that a pure culture of a streptococcus was demonstrated. However, for the purpose of the experiments purity of cultures and analysis of microörganisms was deemed superfluous. To obtain from a tonsil (Case 267) "practically a pure culture" sufficed these authors to demonstrate the elective affinity of some undetermined type of streptococcus for the spinal ganglia. The material was obtained from the tonsils, gums or sputum of cases showing herpes zoster in various parts of the body. After brief growth of the collected material the culture, mixed or pure, was inoculated into animals. In this manner 10 cases, although the author in his summary speaks of 11 cases, in which some clinical data are given, are

dealt with. In all at least 102 animals were treated but on 83 of these were used by the authors in making up their table of results. It would be interesting to know their findings in the other 19 animals. In 1 case it is claimed that a streptococcus was obtained from the spinal fluid of a case of severe unilateral thoracic herpes zoster. Such an important finding impressed them less than the results obtained in animals by the inoculation of mixed cultures from various sources. Hemorrhages were observed in the posterior ganglia and other tissues. Exactly what constitutes positive results in their animals is hard to say. Herpes is recorded as arising in the skin and eyelids. Apparently herpes in animals and that in man are two distinct conditions. "Rabbit No. 33, injected February 11, 1915, with the growth from 30 c.c. of ascites dextrose tissue broth. February 12, found dead. On removal of the skin several hemorrhagic vesicular hemorrhages were found over the left shoulder. A number of hemorrhagic vesicules were found at the juncture of the mucous membrane of the upper lip and the skin, etc." Lesions were also noted in this case in the tongue, appendix, sigmoid, stomach, liver, and spinal ganglia. Multiple foci of infection were observed in many cases, both in animals dying rapidly and those surviving a longer period. That numerous inflammatory areas were encountered in multiple tissue is, considering the dosage of living organisms, what would be expected in the use of various pathogenic bacteria. It is difficult to understand how these authors can claim elective localization by particular microörganisms in the experiments detailed.

Pathological Reconstruction of Organs (Metallaxis) and its Significance in Chronic Bright's Disease and Arteriosclerosis. — JORES (*Virchows Archiv*, 1916, 221, 14) expresses a general agreement with the classification by Volhard and Fahr particularly as regards the significance of primary renal arteriosclerosis in bringing about the small granular kidney which the Mannheim authors designate the mixed type. This form was claimed to result from the presence of arteriosclerosis and inflammation. Glomerular changes are commonly present either as a true inflammation or in epithelial desquamation within the glomerular capsule. It is difficult to say whether the examples studied by Jores and those by Volhard were the same. The former found evidence of degeneration about the glomerular capillaries. He believed that these changes were secondary to the arterial lesions similar to the atrophic changes which appear in the tubules which he speaks of as an atrophy of disuse. The atrophic changes of the epithelial structures vary, depending upon their position in the tubule. Indirectly the tubular changes result from the circulatory disturbances within the glomeruli. Not uncommonly the atrophy of one portion of the tubule is accompanied by an hypertrophy and hyperplasia in another. The proliferative changes in the tubules are a compensatory response to the degenerative process occurring diffusely in the kidney. The author states that the arteriosclerotic kidney is only distinguished from the mixed type by the degree in which the glomeruli are involved. He does not believe inflammation plays any particular role in either of the conditions. He applies a similar discussion to arteriosclerosis to justify the stand which he has taken in this subject. Inflammation,

he believes, plays only a secondary role. He admits, however, that a variety of arterial lesions of the intima may be included under the term arteriosclerosis. He continues, however, to maintain that his hyperplastic and hypertrophic lesions are the important ones underlying arteriosclerosis. He places no weight upon the development of excess connective tissue in the absence of the described hyperplastic changes. He points out, however, that during the development of a particular pathological lesion in an organ there are commonly other tissue changes which are more or less of a compensatory character. This he names metallaxis. Admitting for arteries that one lesion may be followed by others in neighboring tissues the author is unwilling to supply the name arteriosclerosis to all proliferative and degenerative processes occupying the intima. He still demands a restriction of the term to the type described by himself. Thus, he states, the name arteriosclerosis is to be applied to the metallaxis of the vascular system in which lipoid degeneration and calcification are associated with hypertrophy and compensatory hyperplasia of the intima.

The Liver Changes in Wilson's Disease.—In 1912 Wilson described 12 cases of degeneration of the nucleus lentiformis associated with cirrhosis of the liver. During life the patients exhibited muscle weakness, dysphagia and involuntary, rhythmic, muscular twitching. Since the first description for this disease a number of new reports have been made by others. The majority of authors have commented upon the liver changes as differing from the usual atrophic portal cirrhosis. Some have suggested a congenital process of the liver with regeneration of the parenchyma. GEISSMAR (*Frank. Ztschr. f. Path.*, 1916, xviii, 305) reported a study of 4 cases with autopsy findings. The cases were all males, 3 of them brothers. Particular attention was given to the liver changes observed in 2 of the cases. Ascites was present in 2 cases and icterus in 1. In the liver there were no evidences of necroses though degenerative changes and pigment deposit were to be seen in the liver cells. Cirrhosis was marked. The fibrosis was irregular, often dividing the lobule into islands. Regenerative changes were also quite marked. The type of cirrhosis was not entirely comparable to either portal or syphilitic cirrhosis. The functional disturbances of the liver closely resembled portal cirrhosis. Splenic changes mainly resulted from portal stasis. No analysis was made of the cerebral lesions and no explanation is offered for the concurrent liver derangement.

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All communications should be addressed to—

DR. GEORGE MORRIS PIERSOL, 1913 Spruce St., Phila., Pa., U. S. A.

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